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Development of Anterior Cingulate Functional Connectivity from Late Childhood to Early Adulthood

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Human cerebral development is remarkably protracted. Although microstructural processes of neuronal maturation remain accessible only to morphometric post-mortem studies, neuroimaging tools permit the examination of macrostructural aspects of brain development. The analysis of resting-state functional connectivity (FC) offers novel possibilities for the investigation of cerebral development. Using seed-based FC methods, we examined the development of 5 functionally distinct cingulate-based intrinsic connectivity networks (ICNs) in children ($n = 14$, 10.6 ± 1.5 years), adolescents ($n = 12$, 15.4 ± 1.2) and young adults ($n = 14$, 22.4 ± 1.2). Children demonstrated a more diffuse pattern of correlation with voxels proximal to the seed region of interest (ROI) ("local FC"), whereas adults exhibited more focal patterns of FC, as well as a greater number of significantly correlated voxels at long distances from the seed ROI. Adolescents exhibited intermediate patterns of FC. Consistent with evidence for different maturational time courses, ICNs associated with social and emotional functions exhibited the greatest developmental effects. Our findings demonstrate the utility of FC for the study of developing functional organization. Moreover, given that ICNs are thought to have an anatomical basis in neuronal connectivity, measures of FC may provide a quantitative index of brain maturation in healthy subjects and those with neurodevelopmental disorders.

Keywords: anterior cingulate, BA 25, development, functional connectivity, self-regulation

Introduction

Neuronal Maturation and Cerebral Development

Histological and stereological post-mortem studies of human and nonhuman primate brain have provided profound insights into the microstructural processes of neuronal maturation and the development of cerebral functional organization. These studies suggest that postnatal cerebral development is marked by a period of "exuberant" and redundant synaptic connectivity, likely reflecting an overproduction of dendrites, dendritic spines, and axons during the perinatal period (Huttenlocher et al. 1982; LaMantia and Rakic 1994; Petanjek et al. 2008). This superabundant connectivity is maintained throughout childhood, such that synaptic density remains at higher-than-adult levels until about the onset of puberty, from which time there is a net elimination of synapses. As a result of such "pruning," the density of synapses declines by ~40% during adolescence, before reaching a plateau in adulthood (Huttenlocher 1979; Huttenlocher et al. 1982; Rakic et al. 1986; Bourgeois and Rakic 1993; Bourgeois et al. 1994; Rakic et al. 1994). The rate at which pruning occurs varies across the cerebrum: the decline in synaptic density appears to begin earlier in visual and somatosensory cortex than in prefrontal cortex (Bourgeois et al. 1994; Huttenlocher and Dabholkar 1997). Neuronal myelination, another key process in postnatal neuronal maturation, appears to follow a similarly protracted and regionally specific time course. Though few studies have examined this process in human brain, post-mortem analyses suggest that myelination begins near the end of the second trimester of fetal life, increases intensely during the first 2 decades of life, then continues at a slower rate into middle adulthood, with the most protracted development in the frontal and temporal lobes (Yakovlev and Lecours 1967; Brody et al. 1987; Benes et al. 1994).

That the nonlinear developmental pattern of synaptogenesis and synaptic elimination is associated with concurrent functional development of neuronal networks is suggested by the observation that neurotransmitter innervation and receptor density follow a similar developmental trajectory throughout the cortex (Goldman-Rakic and Brown 1982; Lidow et al. 1991; Lidow and Rakic 1992; Rosenberg and Lewis, 1995; Lambe et al. 2000). Early synaptic redundancy has been suggested as the basis for the emergence of cognitive function in the infant (Goldman-Rakic 1987; Petanjek et al. 2008), as well as the synaptic plasticity that characterizes children's ability for learning and recovery from injury (Changeux and Danchin 1976). Though associated with the loss of this superabundant plasticity, synaptic pruning may enable more efficient information transfer across spatially distal regions in the brain, and may therefore underlie the development of mature cognitive function (Changeux and Danchin 1976; Goldman-Rakic 1987; Huttenlocher 1990; Paus et al. 1999).

Magnetic Resonance Imaging Studies of Cerebral Development

The emergence of magnetic resonance imaging (MRI) and more recently, diffusion tensor imaging (DTI) have permitted the noninvasive examination of age-related structural changes in vivo (e.g., Giedd et al. 1999; Paus et al. 1999; Sowell et al. 1999; Sowell et al. 2003; Gogtay et al. 2004). These studies have been largely consistent with the human and nonhuman morphometric data: the observed age-related increases in white matter (WM) are primarily thought to reflect progressive myelination, whereas age-related decreases in gray matter are thought to reflect both synaptic pruning and myelination (Bartzokis et al. 2001; Giedd 2004; Gogtay et al. 2004; Sowell et al. 2004). Specifically, studies have observed that global WM volume increases linearly between the ages of 4 and 22 years (Giedd et al. 1999), with continued increases observed up to the fifth decade of life (Bartzokis et al. 2001; Sowell et al. 2003).

In contrast, gray matter volumes follow a nonlinear developmental trajectory whereby peak volumes are attained at approximately 10–12 years (Giedd et al. 1999), followed by a significant decline throughout adolescence and adulthood (Sowell et al. 2001, 2003). Consistent with regional differences in the onset of declines in synaptic density (Bourgeois et al. 1994; Huttenlocher and Dabholkar 1997), several studies have observed regional differences in the onset of gray matter loss, which appears to occur earliest (at around the onset of puberty) in the primary sensory and motor areas and latest (at about the end of adolescence, and as late as ~30 years) in lateral prefrontal and temporal cortices (Sowell et al. 1999, 2001, 2003; Gogtay et al. 2004).

DTI studies demonstrate a complementary pattern of results. The most commonly reported measure in DTI studies is fractional anisotropy (FA), which is thought to reflect the diameter, density and myelination of WM fibers that connect brain areas (Snook et al. 2005; Giorgio et al. 2008). Age-related increases in FA have been observed both in whole-brain averages and in several principal WM pathways, including the corpus callosum, and the inferior fronto-occipital, superior longitudinal and uncinate fasciculi, during late childhood, adolescence and early adulthood (Olesen et al. 2003; Snook et al. 2005; Zhang et al. 2005; Liston et al. 2006; Eluvathingal et al. 2007; Giorgio et al. 2008). Finally, consistent with the idea that structural changes in white and gray matter underlie maturation of cognitive function, several studies have observed correlations between structural changes thought to reflect myelination and synaptic pruning and age-related improvements in measures of cognitive functions such as working memory (Sowell et al. 2001; Olesen et al. 2003; Nagy et al. 2004; Liston et al. 2006).

Age-related changes in measures of brain activation also appear consistent with the reported structural changes. Using positron emission tomography, Chugani et al. (1987) showed that regional cerebral glucose metabolism increased from birth, peaking at 1.4 times the final level at ~9 years, followed by a decline to adult levels throughout the teenage years. A similar result was observed in monkeys (Jacobs et al. 1995), supporting the idea that the age-related changes in glucose metabolism reflect the periods of synaptic and neurotransmitter excess and subsequent elimination observed in anatomical studies (e.g., Huttenlocher 1979; Rakic et al. 1986). More recently, blood oxygen level–dependent (BOLD) functional MRI (fMRI) studies have shown that, relative to adults, young children typically activate larger and more diffuse regions of prefrontal cortex when performing tasks that require attentional control, such as Go/NoGo or Flanker tasks (Casey et al. 1997; Bunge et al. 2002; Tamm et al. 2002; Durston et al. 2006). The pattern of diffuse activation is consistent with the idea that, in children, these tasks activate immature and inefficient functional networks, whereas the focal activations exhibited by adults may be a functional consequence of synaptic elimination (Luna and Sweeney 2004; Casey et al. 2005). Accordingly, studies have shown that the BOLD activity that correlates with task performance becomes more focal with age, whereas activity not correlated with performance decreases with age (Brown et al. 2005; Durston et al. 2006).

Functional Connectivity

Despite the progress made by these functional imaging studies, the maturational changes occurring on the level of large-scale functional networks have remained somewhat elusive. Functional connectivity (FC) analyses of the brain's spontaneous activity may offer an alternative means to examine the development of these networks. FC analyses, which detect temporal correlations between "spatially remote neurophysiological events" (Friston et al. 1993), reveal patterns of correlated ultra-low frequency (<0.1 Hz) spontaneous BOLD activity within a number of functionally distinct processing systems (Greicius and Menon 2004; Damoiseaux et al. 2006; Fransson 2006; Margulies et al. 2007; Di Martino et al. 2008), in human infants (Fransson et al. 2007), and in other species such as chimpanzees, macaques and rats (Rilling et al. 2007; Vincent et al. 2007; Kannurpatti et al. 2008). The networks detected in these studies have been termed resting-state networks (De Luca et al. 2006) or, more appropriately, intrinsic connectivity networks (ICNs, Seeley et al. 2007), given their detection across a variety of states, including task performance. These networks show striking spatial correspondence to known functional systems (Biswal et al. 1995; Damoiseaux et al. 2006; Fox et al. 2006; Margulies et al. 2007), and patterns of coactivation observed in task-based studies (Toro et al. 2008), suggesting that their spontaneous activity reflects functionally relevant communications among neurons (Leopold et al. 2003; Buzsaki 2006). It is increasingly thought that this spontaneous activity may serve to maintain network integrity by reinforcing the synaptic connections that subserve the network's typical functioning during awake states (Fox and Raichle 2007; Pinsk and Kastner 2007). As such, FC approaches may provide a novel way to quantify brain development and maturation.

Although many studies have examined the structure and organization of ICNs in adults, few have examined how ICNs change with development. Fair et al. (2007) recently used region-of-interest-based interregional FC and graphical methods in a large sample of children, adolescents and adults to examine the development of 2 ICNs subserving cognitive control functions. Fair et al. demonstrated that maturation of these networks involved both segregation (a reduction in short-range local correlation strength) and integration (an increase in the strength of long-range FC with other brain regions). In a subsequent study using a seed-based approach, Fair et al. (2008) also demonstrated increasing FC between components of the default-mode network with age.

Anterior Cingulate FC and Development

Fair et al.'s findings suggest that FC approaches may be fruitful when applied to the examination of brain development and maturation. Moreover, given that the ICNs detected using FC analyses are thought to have an anatomic basis in neuronal connectivity (Andrews-Hanna et al. 2007; Fox and Raichle 2007; Vincent et al. 2007; Greicius et al. 2008), measures of FC may even provide a quantitative index of brain maturation. Here, we explore this possibility, by examining the development of 5 cingulate-based ICNs. The anterior cingulate cortex (ACC) is at the center of the brain's self-regulatory system, integrating inputs from diverse sources in order to regulate responses and guide behavior (Bush et al. 2000; Paus 2001; Amodio and Frith 2006). As such, development of the functional organization of anterior cingulate-based networks is likely to be an essential step in the cerebral maturation that underlies cognitive, social and emotional development.

In a recent resting-state fMRI study (Margulies et al. 2007), we examined cingulate FC by eliciting the ICNs associated with

16 seed regions of interest (ROIs) systematically placed throughout the ACC in 2 arrays designated superior (S) and inferior (I) (Fig. 1*A*). Our findings were highly consistent with anatomical and neuroimaging studies of functional differentiation within the ACC. In the present study, we selected 5 of those ACC seeds for examination in a developmental context, maintaining the naming convention used by Margulies et al. to refer to the ACC seeds. Seeds were selected so as to sample 5 principal functions associated with the ACC, and were placed in caudal (S1), dorsal (S3), rostral (S5), perigenual (S7), and subgenual (I9) regions of the ACC. These regions are broadly associated with 5 domains of self-regulatory control, namely, motor control, attentional/cognitive control, conflict monitoring, mentalizing and emotional regulation, respectively (see Fig. 1*A*).

Cognitive developmental studies demonstrate that the processes associated with these broad functional domains undergo considerable change throughout childhood and adolescence, but with differential rates of maturation. Functions associated with motor control and less complex aspects of cognitive control, such as inhibitory control and working memory maintenance, are thought to develop rapidly during childhood (Ridderinkhof et al. 1997; Rueda et al. 2004, 2005; Davidson et al. 2006). In contrast, more sophisticated aspects of attentional control, as well as many of the evaluative, social

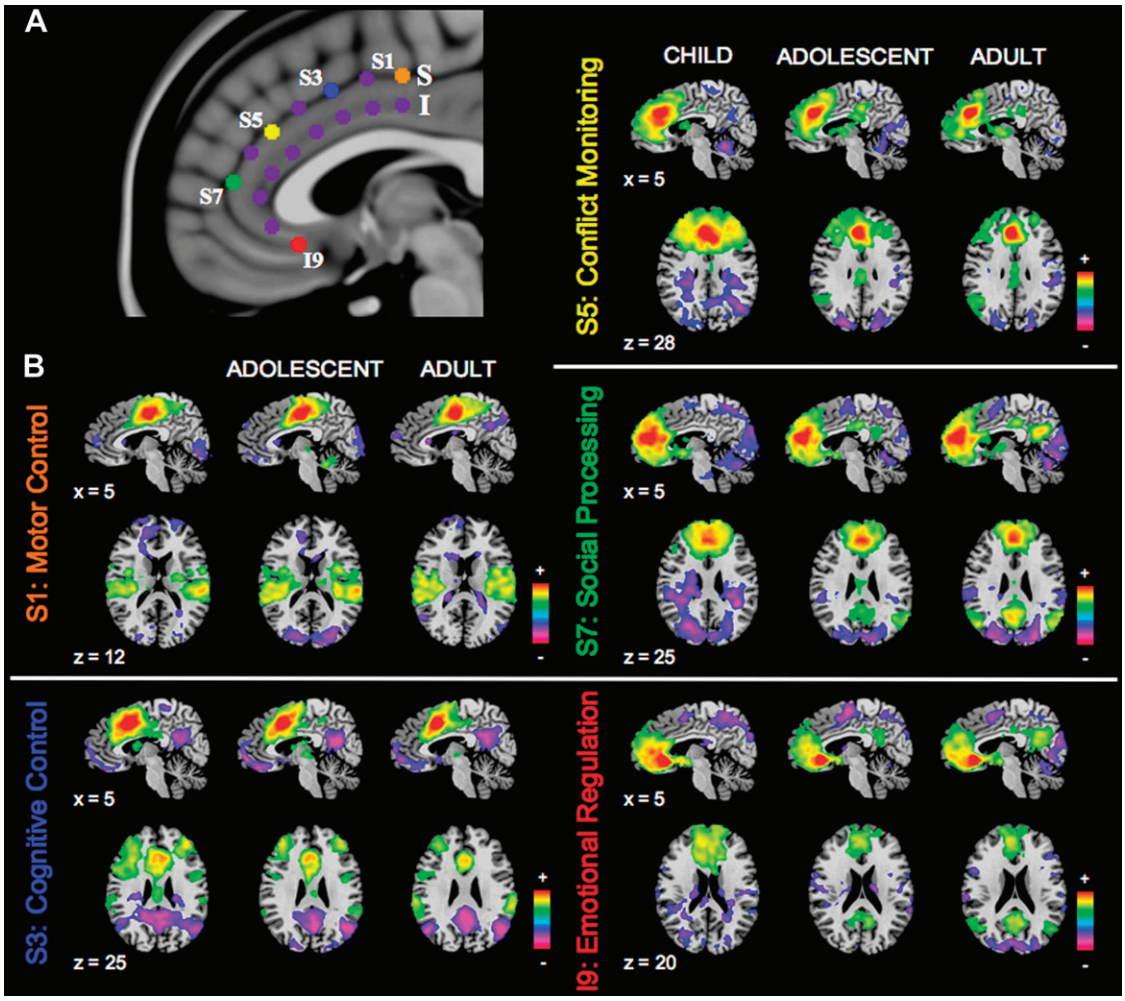

Figure 1. (*A*) Margulies et al. (2007), seeded the ACC at 16 coordinates along 2 separate rows: an inferior row (I), located 5 mm from the corpus callosum, starting at $y = -10$ (I1), and spaced 10 mm apart along a curve traced parallel the corpus callosum; and a superior row (S), located 15 mm from the corpus callosum along radial axes extending from each of the 7 inferior seeds. Here, we examined the ICNs elicited by 5 of those seeds: S1 (orange), S3 (blue), S5 (yellow), S7 (green), and I9 (red). Seed S1 (MNI coords: $x = 5$, $y = -10$, $z = 47$), in the caudal ACC, was located in a region critically involved in movement execution and the control of motor behavior (Dum and Strick 1991; Carmichael and Price 1995b; Paus 2001; Chouinard and Paus 2006). The dorsal ACC (dACC), the location of seed S3 ($x = 5$, $y = 14$, $z = 42$) is thought to play a central role in the top-down control of attention, and is commonly activated during working memory, response selection and inhibition, and in response to task cues (e.g., Posner and Petersen 1990; Garavan et al. 2002; Wager and Smith 2003; Hester et al. 2004; Milham and Banich 2005; Curtis 2006; Weissman et al. 2006; Nee et al. 2007; Dosenbach et al. 2008). Seed S5 ($x = 5$, $y = 34$, $z = 28$) was located in the rostral section of supragenual ACC, an area typically associated with more evaluative functions than dACC, including monitoring and signaling of conflict or interference, response to errors, reasoning and decision making (Botvinick et al. 1999; Kiehl et al. 2000; Kroger et al. 2002; Garavan et al. 2003; Luo et al. 2003; Botvinick et al. 2004;; Paulus and Frank 2006; Taylor et al. 2006; Lutcke and Frahm 2007). Seed S7 ($x = 5$, $y = 47$, $z = 11$) was located in the perigenual ACC which has been centrally implicated in social cognitive functions such as mentalizing and self-reflection (Johnson et al. 2002; Frith and Frith 2003; Ochsner et al. 2005; Amodio and Frith 2006). Finally, seed I9 ($x = 5$, $y = 25$, $z = -10$) was located in the subgenual ACC, corresponding to BA 25, which is central to a limbic and paralimbic system that subserves emotional responsiveness and regulation and the monitoring of rewarding or punishing outcomes (Drevets et al. 1997; Phan et al. 2002; Knutson et al. 2003; Phillips et al. 2003; Mayberg 2006; Taylor et al. 2006). (*B*) The panels illustrate significant positive (green–red) and negative (blue–pink) connectivity for each ACC seed, for each group (child, adolescent, adult), according to neurological convention (right is right), in Talairach space.

and emotional functions associated with rostral and ventral areas of the ACC continue to undergo substantial development throughout adolescence and into adulthood (Nelson et al. 2003; Ernst et al. 2005; Steinberg 2005; Blakemore and Choudhury 2006; Crone et al. 2006; Davidson et al. 2006; Galvan et al. 2006; Thomas et al. 2007; Hare et al. 2008).

Based on the morphometric, structural and functional evidence reviewed above, we hypothesized that each ACC network would demonstrate age-related differences in FC. Specifically, based on the evidence for net synaptic elimination during adolescence, we predicted a gradual transition in the pattern of correlated voxels, from one dominated by diffuse local (short-distance) correlations in childhood, to one characterized by more focal (spatially limited) local correlations in adulthood. In addition, we expected to observe a greater number of positively correlated voxels at long distances from the seed ROI in adulthood, potentially reflecting the maturation of large-scale functional networks underlying cognition. Finally, we examined the prediction that measures of FC would reveal regional differences in the time course of maturation across the 5 networks, with motor and cognitive networks showing more rapid maturation than social and emotional networks.

Methods

Participants

Children and Adolescents

Fourteen children (mean age:10.6 ± 1.5 years; range: 8.7–12.7; 4 females) and 12 adolescents (mean age: 15.4 ± 1.2 years; range: 13.5–17.0; 5 females) were recruited from the local community. Absence of DSM-IV Axis-I diagnosis was established based on parent interviews using the Schedule of Affective Disorders and Schizophrenia for Children—Present and Lifetime Version.

Young Adults

Fourteen young adults (mean age: 22.4 ± 1.2 years; range: 19.7–24.0; 5 females) were recruited from the local community. All adults had no history of psychiatric or neurological illness as confirmed by a psychiatric clinical interview. Absence of known neurological or chronic medical diseases was required of participants in all age groups. Data from 9 of the adult participants were previously reported by Margulies et al. (2007). The study was approved by the institutional review boards of the New York University School of Medicine and New York University. Signed informed consent was obtained from all participants and their legal guardian (in the case of children and adolescents) prior to participation. Participants received monetary compensation.

Functional Imaging

Functional imaging data were acquired using a research-dedicated Siemens Allegra 3.0 Tesla scanner, located at the NYU Center for Brain Imaging. We obtained a brief (6 min 38 s) "resting-state" scan, comprising 197 contiguous echo planar imaging whole-brain functional volumes (time repetition [TR] = 2000 ms; time echo [TE] = 25 ms; flip angle = 90, 39 slices, matrix = 64 × 64; field of view [FOV] = 192 mm; acquisition voxel size = 3 × 3 x 3 mm). Coverage of the entire cerebellum was not possible in all participants. During this scan participants were asked to relax with their eyes open. A high-resolution T_1-weighted anatomical image was also acquired using a magnetization prepared gradient echo sequence (TR = 2500 ms; TE = 3.93 ms; inversion time = 900 ms; flip angle = 8; 176 slices, FOV = 256 mm).

Image Preprocessing and Individual Analyses

Preprocessing steps of slice timing correction for interleaved acquisition (using Fourier interpolation), motion correction (by aligning each volume to a "base" image using Fourier interpolation) and despiking (detection and reduction of extreme time series outliers using an hyperbolic tangent function) were performed using analysis of functional neuroimages (AFNI, Cox 1996). All other data processing was carried out using FSL (FMRIB Software Library, www.fmrib.ox.ac.uk). Further image preprocessing comprised spatial smoothing (using a Gaussian kernel of full width half maximum 6 mm), mean-based intensity normalization of all volumes by the same factor, temporal bandpass filtering (highpass temporal filtering: Gaussian-weighted least-squares straight line fitting, with sigma = 100.0 s; Gaussian lowpass temporal filtering half-width half maximum [HWHM] 2.8 s) and correction for time series autocorrelation (prewhitening). As a final preprocessing step, each individual's time series was spatially normalized by registration to the MNI152 template (Montreal Neurological Institute), with 1-mm^3 resolution, using a 12 degrees-of-freedom affine transformation.

Movement Parameters

Root-mean-square (rms) movement in each of the cardinal directions (x, y, and z), and rotational movement about 3 axes (pitch, yaw, and roll) was calculated for each participant, and the relationship between mean rms movement and age was examined. Data were also visually inspected for movement-related artifacts.

FC: ROI Selection and Seed Generation

Following the methods outlined in Margulies et al. (2007), we examined the FC of 5 seed ROIs located along the ACC (Fig. 1*A*). Each spherical seed covered 123 voxels in 1 × 1 x 1 mm space with a radius of 3.5 mm. For each participant, we calculated the mean time series of each seed ROI by averaging across all voxels within the seed.

FC: Nuisance Signals

Several nuisance covariates were included in our analyses to control for the effects of physiological processes (such as fluctuations related to cardiac and respiratory cycles) and motion. Specifically, we included 9 additional covariates that modeled nuisance signals from WM and cerebrospinal fluid (CSF), the global signal, as well as 6 motion parameters. The global signal regressor was generated by averaging across all voxels within the brain. To extract the nuisance covariate time series for WM and CSF, we first segmented each individual's high-resolution structural image, using the FSL's FAST segmentation program provided by FSL. The resulting segmented WM and CSF images were then thresholded to ensure 80% tissue type probability. These thresholded masks were then applied to each individual's time series, and a mean time series was calculated by averaging across all voxels within the mask. Finally, the 6 motion parameters were generated by the AFNI motion correction program 3dvolreg.

FC: Statistical Analysis

For each participant, and for each seed ROI, we performed a multiple regression analysis (as implemented in the FSL program FEAT), which included the ACC seed time series and the 9 nuisance covariates as predictors. Time series for the seed ROI were orthogonalized with respect to the nuisance covariates (global signal, CSF, WM, and motion covariates). This analysis produced subject-level maps of all voxels that were significantly positively or negatively correlated with the seed time series.

Group-Level Analyses

Group-level analyses and group comparisons were carried out using a mixed-effects model as implemented in the FSL program FLAME. Corrections for multiple comparisons were carried out at the cluster level for each of the 5 networks using Gaussian random field theory (min $Z > 2.3$; cluster significance: $P < 0.05$, corrected). This group-level analysis produced thresholded Z-score maps ("networks") of positive and negative FC for each seed ROI, for each group separately and for all subjects combined. To test for significant age-group–related differences, direct voxelwise group comparisons were performed using group-level contrasts. These contrasts computed the voxelwise statistical significance of mean group differences in FC, and produced thresholded Z-score maps of those voxels that showed significant

age-related changes in FC with the seed ROI. We divided these changes into 2 classes, based on the group means of parameter estimates representing FC between the seed ROI and the cluster in question. Monotonic age-related changes reflected a unidirectional increase or unidirectional decrease in FC across the groups (i.e., children > adolescents > adults, or children < adolescents < adults, as revealed by the contrasts 1, 0, –1, or –1, 0, 1). Changes that were not unidirectional were classified as nonmonotonic. Group variances were modeled separately in these analyses.

We identified peaks of FC for each network, using the group-level thresholded *Z*-score maps for all subjects combined. Using the peak detection algorithm provided in the AFNI program 3dMaxima, we specified a minimum significance threshold of $Z = 2.3$, and minimum distance between peaks of 10, 2-mm isomorphic voxels. For consistency with the literature, peaks were converted to Talairach coordinates using a nonlinear transformation (Brett et al. 2002). Group-level results were registered to the Talairach brain (Talairach and Tournoux 1988) for presentation purposes.

Voxel Distance Calculations

In addition to voxelwise group comparisons, we conducted a further analysis aimed at elucidating the differences in local (short-range) and distal (long-range) positive FC between groups. For each network, and for each age group, we computed the Euclidean distance between the center of the seed ROI and every other voxel that reached significance in the group-level thresholded *Z*-score map of positive FC (i.e., $Z > 2.3$, cluster significance: $P < 0.05$). These data were separated into 4-mm bins for visualization (see Fig. 4). To confirm any differences observed at this group-map level, we applied the same method at the individual level, and computed the number of significant voxels at specific distances (from 0 to 140 mm in 20-mm bins, see Fig. 5) from the seed ROI for each individual. The number of voxels within a given distance range from a given seed that were significantly correlated with that seed can be viewed as a binomial random variable, for which the "success probability" varies from subject to subject. We therefore regressed the number of such voxels on age group using logistic regression allowing for overdispersion (Collett 2003). The reduction in deviance for such a model compared with the null model can be referred to as a chi-square distribution to test for an overall effect of age group. In addition we fitted separate models to each of the 3 pairs of groups, which allowed us to test pairwise group differences.

Results

Movement Parameters

All but one participant exhibited minimal movement (<1-mm rms, see Supplementary Table 1 for summary statistics), a level comparable to other studies comparing adults and children (e.g., Kang et al. 2003; Wenger et al. 2004; Thomason et al. 2005; Fair et al. 2007; Church et al. 2008). Data were also visually inspected for movement-related artifacts. The one participant who exhibited excess movement, as indicated by mean rms displacement and rotational movement >1 mm, and visual identification of movement-related artifact, was excluded from further analyses. To reflect the loss of this participant, revised details for the analyzed children are as follows: $n = 13$, mean age 10.5 ± 1.5 years, range: 8.7–12.7, 3 females.

Even though movement was minimal, across the entire group there was a significant negative correlation between movement (measured in terms of rms) and age ($n = 39$, $r = -0.465$, $P < 0.01$), as well as rotation and age ($n = 39$, $r = -0.588$, $P < 0.001$). When correlations were performed in each group separately, only the young child group showed a significant negative correlation between rms rotational movement and age ($n = 13$, $r = -0.569$, $P = 0.042$). At this within-group level, no significant correlations were observed for mean rms of displacement. Despite minimal participant movement, motion regressors were included as covariates in the GLM to account for any possible effects of motion on FC.

Functional Connectivity

Overall, the FC maps for each of the 5 ACC ROIs differed systematically from one another, as we expected from the previous FC analysis of Margulies et al. (2007). The patterns of FC observed were also consistent with the broad literature on functional differentiation within the ACC (e.g., Elliott et al. 2000; Braver et al. 2001; Paus 2001; Frith and Frith 2003; Botvinick et al. 2004; Amodio and Frith 2006; Taylor et al. 2007). The results for the adult group were almost identical to those observed by Margulies et al. despite sharing only 9 subjects and comprising a smaller number of participants overall. Most striking, however, were the effects of development on FC, which are described in detail below.

Motor Control—Caudal ACC (S1)

Positive FC. In adults, caudal seed S1 was positively correlated with a bilateral network of posterior frontal, parietal and subcortical regions associated with sensorimotor processes and motor control, including pre- and postcentral cortex, putamen, and thalamus (Paus 2001; Chouinard and Paus 2006) (Figs 1*B* and 2). Peaks of FC (for the map resulting from all 3 groups combined) are provided in Supplementary Table 2. Children and adolescents exhibited patterns of FC that were highly similar to that of the adult group, and voxelwise comparisons revealed a monotonic increase in FC with right superior temporal cortex from childhood (when the correlation is negative) to adulthood (Table 1; see Fig. 2, shown in yellow), but no other significant group differences. A plot of the mean FC between seed S1 and this superior temporal cluster is shown in Figure 3.

Voxel distance calculations. Figure 4 displays the number of voxels that were significantly positively correlated with each seed ROI, in intervals of 4 mm (Euclidean distance) from the center of the seed. These data were computed on the basis of the *group-level* thresholded *Z*-stat maps (min $Z > 2.3$; cluster significance: $P < 0.05$, corrected). We then computed the number of significantly positively correlated voxels at specific distances (from 0 to 140 mm in 20-mm bins, see Fig. 5) from the seed ROI *for each individual* (on the basis of their thresholded *Z*-stat map). To examine group differences in these distance data, we regressed the number of voxels at each interval on age group using overdispersed logistic regression and compared the resultant model to the null model using a chi-square test. We did this for all 3 groups (testing an overall effect of age group), and for all 3 pairings of the groups, to test pairwise group differences. The results of these tests, for each seed ROI and each distance interval, are displayed in Table 2. This test did not reveal any significant overall or pairwise group differences for seed S1.

Negative FC. In adults, seed S1 showed a negative relationship with activity in ventromedial prefrontal cortex (PFC), posterior lateral parietal cortex, posterior cingulate and precuneus, the caudate and superior cerebellum. Children and adolescents demonstrated a slightly different pattern of negative relationships, which also included areas of temporal cortex, the lingual gyrus, and ventromedial PFC. Peaks of negative FC (across all

Table 1

Location of clusters of connectivity (both positive and negative) that differed significantly between groups, for each of the 5 ACC seeds

		Cluster size (μL)	BA	Center of mass		
				x	*y*	*z*
Children > adults						
Positive connectivity						
Seed S3	Bilateral (BL) superior/middle/medial frontal gyri/caudate/putamen*	58 192	6/8/9/46/32	−6	−19	34
Seed S5	BL superior/middle frontal gyrus/ACC*	53 288	6/9/46/24/32	8	−29	25
	Right (R) precentral gyrus/insula	5592	6	42	−5	8
Seed S7	R superior/middle/inferior/medial frontal gyrus/ACC	14 200	44/45/9/10/24	−26	−33	14
	Left (L) superior/medial frontal gyri/ACC *	14 144	9/10/24/32	17	−39	9
Seed I9	BL inferior frontal gyrus/medial/orbital PFC/ACC *	51 152	45/47/12/13/24/25	9	−31	1
Negative connectivity						
Seed S3	L superior/middle temporal gyrus	9952	21/22	44	31	−8
	R superior/middle temporal gyrus	18 832	21/22	−48	26	−4
Seed S5	BL culmen	4952		0	50	−16
	L middle temporal/parahippocampal gyrus	6416	21	38	57	23
	R inferior parietal lobe/angular gyrus/posterior cingulate cortex	17 224	39/40/31	−24	51	26
	L inferior parietal lobe/angular gyrus	5272	40/39	34	26	−11
Seed S7	R caudate/IPL	6232	40	−28	26	23
	R brainstem/culmen	5912		−5	38	−21
Adults > children						
Positive connectivity						
Seed S1	R superior temporal gyrus/lingual gyrus*	25 600	21/22/18	−40	48	−1
Seed S7	R inferior parietal lobe/angular gyrus	4784	39/40	−46	62	27
	L inferior parietal lobe/angular gyrus	4640	39/40	49	62	27
	BL posterior cingulate/precuneus*	15 528	23/31/7	−2	51	25
Seed I9	BL inferior parietal/angular gyrus/precuneus/posterior cingulate cortex*	49 488	23/31/7/39/40	−9	45	23
Negative connectivity						
Seed S1	BL precuneus	6024	7	42	58	37
	L posterior parietal	5112	7	−4	68	38
Children > adolescents						
Positive connectivity						
Seed S3	R precentral gyrus	6192	6	10	−21	37
	BL superior/middle/medial frontal gyrus/caudate	18 920	6/8/9/46	−30	−6	27
Seed S5	BL middle frontal gyrus/ACC	20 296	9/46/24/32	17	−31	22
Seed S7	Left medial PFC/ACC	5992	10/24/32	16	−38	7
Seed I9	Left inferior frontal gyrus/medial/orbital PFC/ACC	19 544	47/12/13/24/25	14	−31	3
Negative connectivity						
Seed S5	R inferior parietal lobe/angular gyrus	5248	39/40	−42	56	36
	L inferior parietal lobe/angular gyrus	4144	39/40	37	59	28
Adolescents > children						
Positive connectivity						
Seed S3	R postcentral gyrus	4280	1/2/3	−5	30	59
Seed S7	BL midcingulate cortex	5296	23	−15	20	26
Negative connectivity						
Seed S1	BL superior frontal gyrus	8264	8/9	2	−32	43
Seed S3	L middle/inferior temporal gyrus	4696	21/22	42	43	−6
Seed I9	R thalamus/caudate/parahippocampal gyrus	5544		−29	41	10
	L inferior parietal lobe/lingual gyrus	8568	40	23	48	21
Adults > adolescents						
Positive connectivity						
Seed S1	R precentral Gyrus	13 936	6/4	−2	83	15
Negative connectivity						
Seed S1	L superior Parietal Lobe	6832	7	−6	12	14
	BL caudate/putamen/thalamus	10 856		36	60	37
Adolescents > adults						
Positive connectivity						
Seed S7	L anterior insula/inferior frontal gyrus	4632	44/47/12	31	−17	−7
Seed I9	BL medial precentral cortex	4480	6	6	16	51
Negative connectivity						
Seed S1	BL cuneus/middle occipital gyrus	5264	18/19	−51	12	34
Seed S3	BL parahippocampal gyrus/cuneus	3608	18/19	14	59	2
	R cuneus	4648	18/19	−22	82	20
Seed S5	BL parahippocampal gyrus/lingual gyrus	9648	18/19	4	49	−3

Note: Coordinates are reported in Talairach space. Positive coordinates denote right, anterior and superior. *Indicates the clusters plotted in Figure 3. BL, bilateral.

subjects) are provided in Supplementary Table 3. A significant age-related increase in negative FC with parietal areas—left inferior and superior parietal cortex and precuneus—was observed (Fig. 2, shown in cyan; Table 1).

Attentional/Cognitive Control—Dorsal ACC (S3)

Positive FC. Consistent with studies of cognitive control (Braver et al. 2001; Milham et al. 2001; Dosenbach et al. 2006;

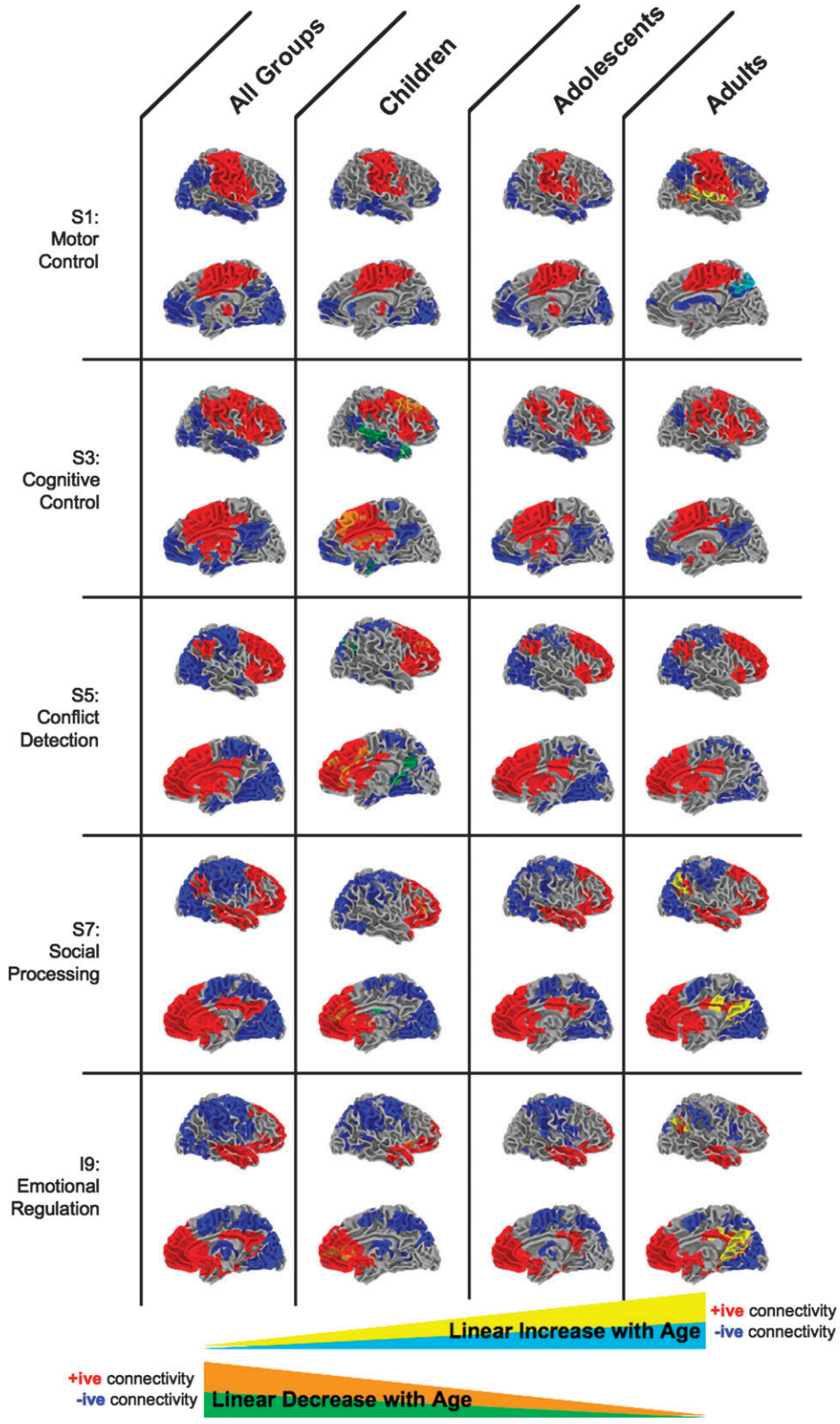

Figure 2. Significant positive (red) and negative (blue) right-hemisphere connectivity for each ACC seed, for each group (Children, Adolescents, Adults), and across all subjects combined (All Groups). Regions of age-related monotonic decreases in positive connectivity are indicated in orange and age-related monotonic decreases in negative connectivity are indicated in green (on the children's maps). Age-related monotonic increases in positive connectivity are indicated in yellow and age-related monotonic decreases in negative connectivity are indicated in cyan (on the Adults' maps). Surface maps were generated using SUMA (Saad et al. 2004) in Talairach space.

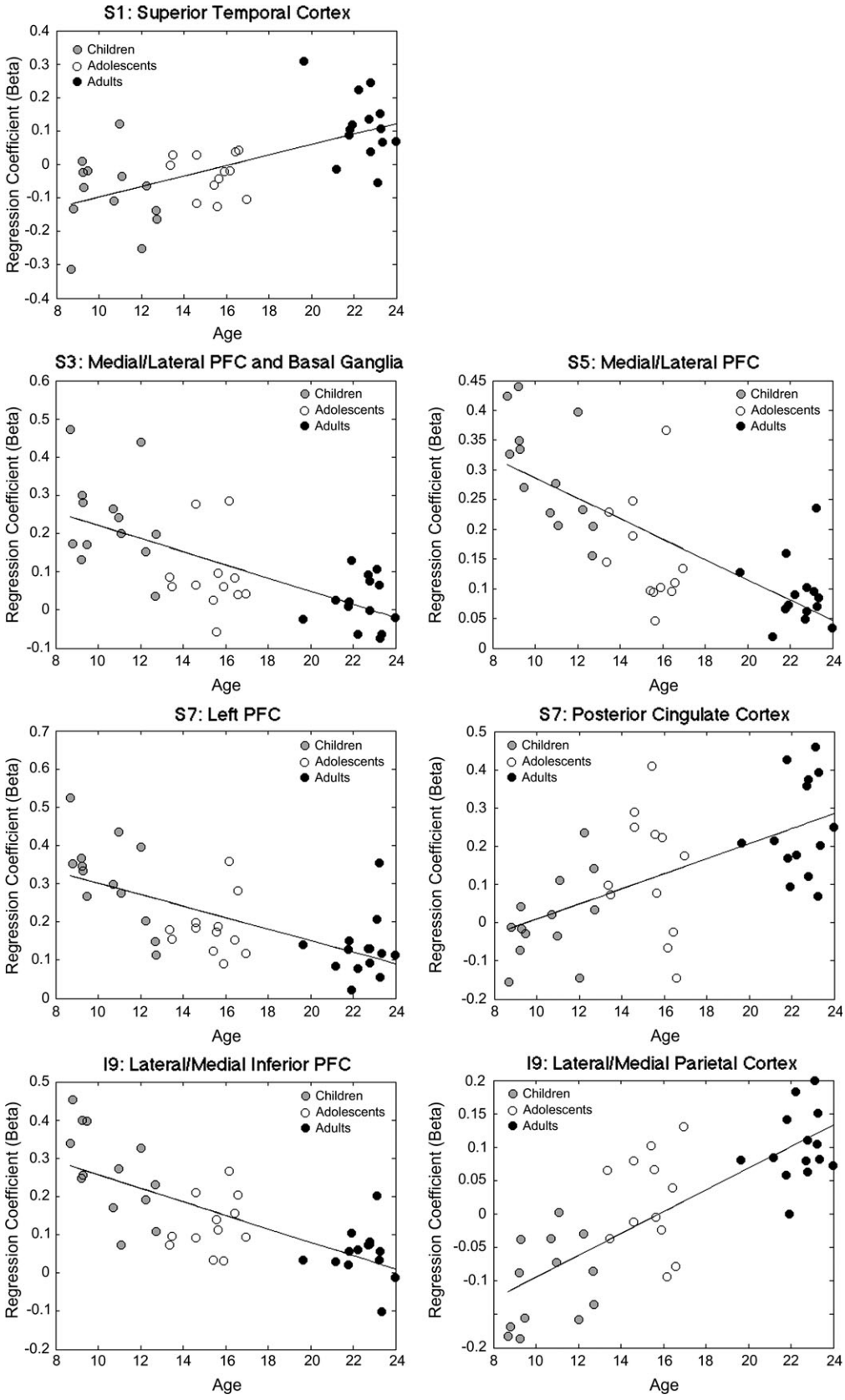

Figure 3. The plots display the mean regression coefficient (reflecting FC) between each seed ROI and an example cluster that demonstrated significant group differences in connectivity. The specific clusters plotted are indicated by a * in Table 1.

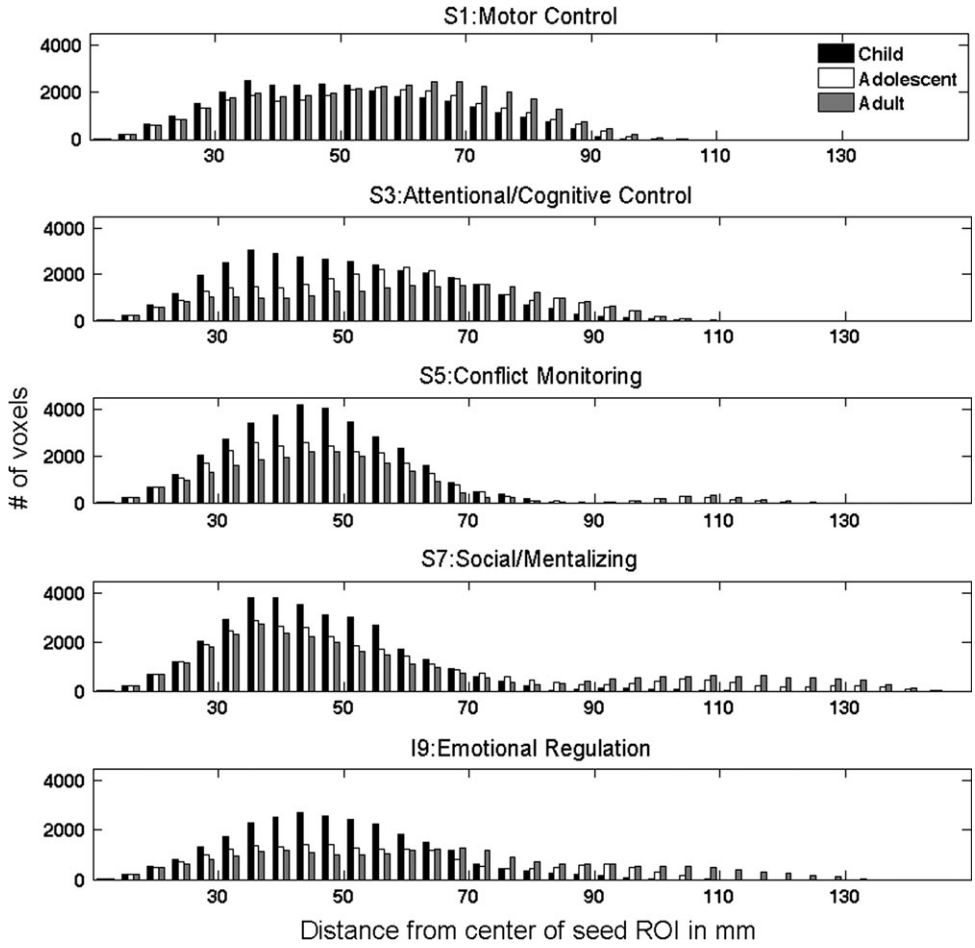

Figure 4. The histograms display, in intervals of 4 mm (Euclidean distance) from the center of the seed ROI, the number of voxels that were significantly correlated with the seed ROI, for each network and for each group. These distance data were computed on the basis of the group-level thresholded *Z*-stat maps (min $Z > 2.3$; cluster significance: $P < 0.05$, corrected).

Nee et al. 2007) the dorsal seed (S3) exhibited positive FC with bilateral areas of superior medial PFC (including dorsal ACC and presupplementary motor area/supplementary motor area), lateral PFC (dlPFC, vlPFC, premotor), insula and inferior parietal cortex (supramarginal gyrus) in adults (Figs 1*B* and 2; peaks of FC are listed in Supplementary Table 4). In children, a greater degree of FC with other prefrontal regions proximal to the S3 seed was observed, particularly with regions in the left hemisphere (see Fig. 1*B*). Direct voxelwise comparisons revealed an age-related monotonic decrease in FC between S3 and areas of superior and anterior medial and superior lateral PFC, bilaterally, extending into the caudate and putamen (Fig. 2, in orange; Table 1). The mean FC between seed S3 and this prefrontal/basal ganglia cluster is plotted in Figure 3.

Voxel distance calculations. Testing for group differences in the distance between the center of seed S3 and every other significantly positively correlated voxel revealed a significant overall effect of age group at short distances only (0–20 mm and 21–40 mm; see Table 2, Figs 4 and 5). Direct pairwise comparisons suggest that although the differences between children and adults, and between children and adolescents (for the shortest distance only) were significant, there were no significant differences between adolescents and adults (Table 2).

Negative FC. In adults, there was a negative relationship between the S3 seed and a number of regions broadly recognizable as the default-mode network. The negative networks for children and adolescents were similar to those of adults but less clearly delineated; additional negative relationships between S3 and regions in the superior temporal and lateral occipital cortices were observed. Peaks of negative FC (across all subjects) are provided in Supplementary Table 5. Voxelwise comparisons revealed a decrease in negative FC between S3 and bilateral temporal areas, bilaterally, with age (Fig. 2, in green; Table 1).

Conflict Monitoring—Rostral ACC (S5)

Positive FC. In line with studies of conflict monitoring and decision making (Paulus et al. 2002; Botvinick et al. 2004), the rostral seed S5 was positively correlated with bilateral regions of medial PFC, frontal pole, midcingulate cortex and insula, and right dlPFC, vlPFC and right inferior parietal cortex (angular gyrus) in adults (Figs 1*B* and 2; for peaks of FC, see Supplementary Table 6). Children showed a diffuse pattern of FC with almost all areas of lateral and medial PFC and anterior insula, but no significant FC with midcingulate and inferior parietal areas. Adolescents showed an intermediate pattern of FC, sharing aspects of the patterns shown by both children and

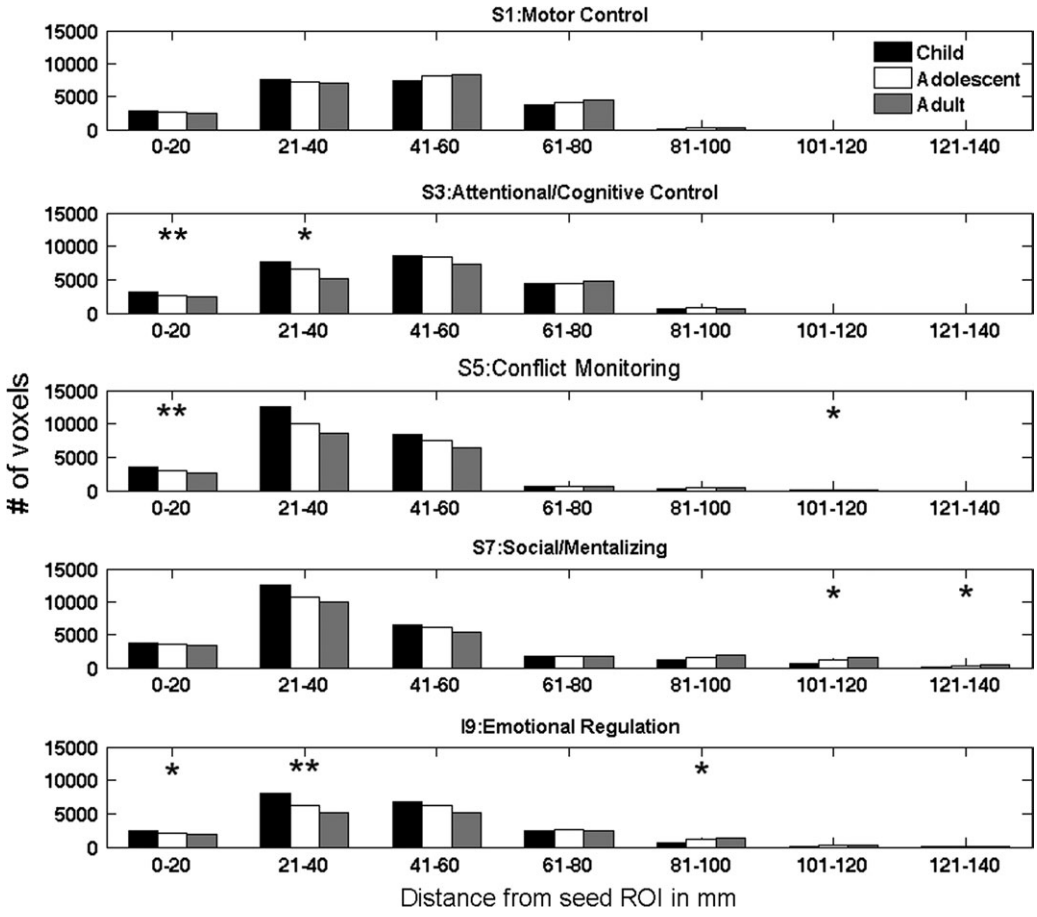

Figure 5. The histograms display, in intervals of 20 mm (Euclidean distance) from the center of the seed ROI, the number of voxels that were significantly correlated with the seed ROI, for each network. These data were computed by calculating the number of significantly correlated voxels in each distance bin, for each *individual* (min $Z > 2.3$; cluster significance: $P < 0.05$, corrected). Significant effects of group are indicated on the histogram with a star: $^{*}P < 0.05$; $^{**}P < 0.01$. *P* values are uncorrected for multiple comparisons.

adults. Voxelwise comparisons revealed a monotonic decrease in FC between the S5 seed and areas of superior and anterior medial and lateral PFC, particularly in the left hemisphere (Fig. 2, shown in orange; Table 1). A plot of the mean FC between seed S5 and this prefrontal cluster is shown in Figure 3.

Voxel distance calculations. There was a significant overall effect of group on the distance between the center of seed S5 and all other significantly positively correlated voxels for short distances only (0–20 mm and 21–40 mm; see Table 2, Figs 4 and 5). Pairwise comparisons again suggest that although the differences between children and adults, and between children and adolescents were significant, there were no significant differences between adolescents and adults (Table 2).

Negative FC. In adults, the S5 seed elicited well-defined negative correlations with bilateral superior parietal lobe and cuneus, bilaterally. Additional negative relationships were observed between S5 and sensorimotor cortex (pre/postcentral gyri), and middle and inferior temporal and fusiform gyri. Children and adolescents showed a similar pattern of negative FC, but more diffuse and comprising more extensive regions of the parietal, occipital and temporal lobes (Figs 1*B* and 2). Peaks of negative FC (across all subjects) are listed in Supplementary Table 7. Voxelwise comparisons revealed age-related decreases in negative FC between S5 and bilateral lateral parietal and posterior cingulate areas and the superior cerebellum (Fig. 2, shown in green; Table 1).

Social Processing—Perigenual ACC (S7)

Positive FC. In adults, perigenual seed S7 was positively correlated with extensive bilateral regions of ventro- and dorsomedial PFC, superior PFC, temporoparietal cortex (angular gyrus), inferior temporal cortex, the posterior cingulate and precuneus, and the dorsal and ventral striatum (Supplementary Table 8), consistent with areas identified in studies of mentalizing (Frith and Frith 2003). As Figures 1*B* and 2 illustrate, children demonstrated a striking lack of the posterior components of this network, while also demonstrating more diffuse FC in frontal areas proximal to seed S7. Voxelwise comparisons revealed age-related monotonic increases in FC between S7 and bilateral regions of inferior parietal cortex and precuneus (Fig. 2, shown in yellow), whereas monotonic decreases in positive FC between S7 and orbital, dorsolateral, ventrolateral, and dorsomedial portions of PFC, bilaterally, were also observed (Fig. 2, shown in orange; see Table 1). Figure 3 plots the mean FC between seed S7 and 2 of the clusters that showed age-related changes in FC: the left prefrontal and posterior cingulate clusters.

Table 2

Chi-square and *P* values for models testing for the overall effect of age group, and pairwise group comparisons, on the number of significantly positively correlated voxels at specific distances (from 0 to 140 mm in 20-mm bins) from the seed ROI

	Distance from center of seed ROI						
	0–20 mm	21–40 mm	41–60 mm	61–80 mm	81–100 mm	101–120 mm	121–140 mm
Overall effect of Group (χ^2 with df = 2)							
S1: motor control	2.87 (0.24)	0.48 (0.78)	1.15(0.56)	1.58 (0.45)	0.73 (0.69)	0.06 (0.97)	—
S3: cognitive control	10.4 (0.005)	9.01 (0.011)	1.6 (0.45)	0.73 (0.69)	1.1 (0.58)	—	—
S5: conflict monitoring	13.1 (0.001)	8.31 (0.016)	4.21 (0.12)	0.38 (0.82)	4.39 (0.11)	6.66 (0.036)	—
S7: social/mentalizing	4.17 (0.12)	4.07 (0.13)	1.92 (0.38)	0.29 (0.86)	3.38 (0.18)	6.76 (0.034)	7.5 (0.023)
I9: emotional regulation	6.16 (0.046)	18 (0.0001)	3.7 (0.157)	0.24 (0.886)	7.62 (0.022)	5.27 (0.072)	1.12 (0.572)
Significant ($P < 0.05$) pairwise comparisons (χ^2 with df = 1)							
S1: motor control	—	—	—	—	—	—	—
S3: cognitive control	Children > adults; Children > adolescents	Children > adults	—	—	—	—	—
S5: conflict monitoring	Children > adults; Children > adolescents	Children > adults	—	—	—	Adolescents > children	—
S7: social/mentalizing	Children > adults	—	—	—	Adults > children	Adults > children	Adults > children
I9: emotional regulation	Children > adults	Children > adults; children > adolescents	—	—	Adults > children; Adolescents > children	Adolescents > children	—

Note: *P* values are uncorrected for multiple comparisons.

Voxel distance calculations. There was a significant overall effect of group on the distance between the center of seed S7 and all other significantly positively correlated voxels at both short (0–20 mm) and long distances (101–120 mm and 121–140 mm; see Table 2, Figs 4 and 5). In direct comparisons only the differences between children and adults were significant (Table 2).

Negative FC. As observed previously (Margulies et al. 2007), the S7 seed was negatively related to activity in regions that were positively related to the caudal and dorsal seeds (S1 and S3), including lateral prefrontal and premotor cortices, dorsal ACC, and lateral parietal and medial occipital cortices, areas typically thought to subserve higher order motor and attentional control processes (see Supplementary Table 9 for peaks of negative FC, across all subjects). Voxelwise comparisons revealed monotonic decreases in negative FC between S7 and subcortical areas; caudate, brainstem, and cerebellum (Fig. 2, shown in green, see Table 1), whereas monotonic increases in negative FC were observed between S7 and superior occipital cortex (Fig. 2, shown in cyan, see Table 1).

Emotional Regulation—Subgenual ACC (I9)

Positive FC. In line with studies of emotional processing and regulation (Drevets et al. 1997; Ochsner and Gross 2005), seed I9, located in the subgenual ACC region corresponding to Brodmann's area (BA) 25, was associated with an extensive pattern of correlated activity in bilateral limbic and paralimbic structures, including the amygdala, regions of the medial temporal lobe including the hippocampus, the orbitofrontal cortex (OFC), as well as the ventral striatum, superior frontal cortex, posterior cingulate, precuneus, and the angular gyrus (Figs 1*B* and 2; Supplementary Table 10). As with the more superior seed S7, children lacked the posterior components of this network, while also demonstrating increased local FC. Voxelwise comparisons revealed monotonic increases in FC between I9 and lateral parietal cortex, the precuneus and posterior cingulate (Fig. 2, in yellow, see Table 1), and monotonic decreases in FC between the I9 seed and regions of PFC, primarily medial and lateral orbitofrontal regions (Fig. 2, shown in orange; see Table 1). The mean FC between seed I9 and these 2 clusters is plotted in Figure 3.

Voxel distance calculations. There was a significant overall effect of group on the distance between the center of seed I9 and all other significantly positively correlated voxels at both short (0–20 mm and 21–40 mm) and long distances (81–100 mm, see Table 2, Figs 4 and 5). In direct comparisons the differences between children and adolescents, and children and adults were significant, but there were no significant differences between adolescents and adults (Table 2).

Negative FC. In adults, the I9 seed showed a pattern of negative FC that was highly similar to S7, and was negatively correlated with a network of regions that is broadly considered to support attentional and motor control (see Supplementary Table 11 for peaks of negative FC). Children and adolescents exhibited a more extensive pattern of negative correlations than adults, and voxelwise comparisons revealed that there was a monotonic decrease in negative FC between I9 and the precentral gyrus with age (Fig. 2, shown in green, Table 1).

Nonmonotonic changes in FC. In addition to the monotonic increases and decreases in FC, several nonmonotonic changes were revealed in the direct contrasts between children and adolescents, and adolescents and adults. A nonmonotonic relationship was observed for FC between S1 and right precentral cortex. Although both children and adults demonstrated positive FC with this area, adolescents showed no significant FC. Conversely, adolescents demonstrated greater positive FC between S1 and the putamen and thalamus, bilaterally, relative to children and adults, and with bilateral medial lingual gyrus, relative to adults.

For seed S3, adolescents demonstrated increased positive FC with right sensorimotor cortex, relative to children and a pattern of negative FC with bilateral regions of the cuneus, and the fusiform and parahippocampal gyri that was not present for either children or adults. A similar pattern of increased negative FC with parahippocampal and middle temporal areas in adolescents was observed for S5.

Discussion

We examined the development of 5 functionally distinct cingulate-based ICNs from late childhood (8–12 years) through

adolescence (13–17 years) to early adulthood (19–24 years). These networks were associated with 5 domains of self-regulatory control: 1) motor control, 2) attentional/cognitive control, 3) conflict monitoring and error processing, 4) mentalizing and social processing, and 5) emotional regulation. The patterns of FC associated with each of the ACC seeds were consistent with the extant literature examining these functions and their underlying neural bases (e.g., Drevets et al. 1997; Elliott et al. 2000; Braver et al. 2001; Milham et al. 2001; Paus 2001; Garavan et al. 2002; Frith and Frith 2003; Phillips et al. 2003; Botvinick et al. 2004; Ochsner et al. 2005; Amodio and Frith 2006; Taylor et al. 2007).

Across the 5 networks, children demonstrated a pattern of diffuse correlations with voxels proximal to the seed ROI (i.e., local FC), whereas adults exhibited more focal patterns of local FC. Furthermore, adults exhibited a greater number of significant correlations between the seed ROI and distal voxels, relative to children. Adolescents exhibited an intermediate pattern of FC that shared characteristics of the patterns of both adults and children. Overall, these developmental patterns are consistent with morphometric and structural neuroimaging evidence suggesting that the adolescent period is marked by a significant net decline in the density of synapses across the brain (Huttenlocher 1979; Huttenlocher et al. 1982; Rakic et al. 1986; Bourgeois and Rakic 1993; Bourgeois et al. 1994; Rakic et al. 1994; Giedd et al. 1999; Sowell et al. 2003). These data are also consistent with functional neuroimaging studies that have demonstrated an age-related shift from diffuse to focal task-evoked activation patterns (Durston and Casey 2006; Durston et al. 2006). Furthermore, our findings are consistent with 2 recent developmental studies of FC (Fair et al. 2007, 2008), which reported that maturation of ICNs reflects a reduction in short-range local correlation strength and an increase in the strength of long-range FC.

Development of FC did not follow a uniform trajectory across all functional networks. The perigenual (S7) and subgenual (I9) networks associated with complex social and emotional processing exhibited the greatest number of long-range connections in adults. The ICNs associated with these seeds also exhibited the greatest developmental effects in terms of both monotonic increases in long-range FC and monotonic decreases in diffuse local FC. The differential time course of maturation among the 5 cingulate networks is consistent with empirical evidence of an extended developmental course for social and emotional functions, relative to functions related to motor and attentional control (Nelson et al. 2003; Ernst et al. 2005; Blakemore and Choudhury 2006; Crone et al. 2006; Galvan et al. 2006; Thomas et al. 2007).

Local and Long-Distance FC

We observed 2 primary patterns of developmental change in ACC FC that are consistent with morphometric and structural neuroimaging studies of the development of cerebral functional organization. The first developmental change we observed was with regard to what we defined as local FC, that is, the pattern of correlations between the seed ROI and proximal voxels ($\leq$40 mm). Although the ICNs of children were characterized by widespread (diffuse) FC between the seed ROI and proximal voxels, the ICNs of adults demonstrated a more focal (spatially limited) pattern of FC. This type of developmental transition has previously been termed "segregation" by Fair et al. (2008, 2007), and can be observed in Figure 1*B* and 2 (see regions colored orange), as well as in the histograms displayed in Figures 4 and 5. The second developmental change we observed was a significant increase in the number of significantly correlated voxels at long distances (>70 mm) from the seed ROI (see regions colored yellow in Fig. 2, and see also Figs 4 and 5). Fair et al. (2008, 2007) termed this type of change in FC "integration," to describe the incorporation of additional regions into an ICN with increasing age.

These patterns of age-related change are consistent with evidence that the adolescent period is marked by a significant net decline in the density of synapses across the brain (Huttenlocher 1979; Huttenlocher et al. 1982; Rakic et al. 1986; Bourgeois and Rakic 1993; Bourgeois et al. 1994; Rakic et al. 1994). Although synaptic pruning may correspond most closely to the transition from diffuse to focal FC, the microstructural changes associated with synaptic pruning, together with neuronal myelination, are also likely to underlie the increases in long-distance FC, as these processes are thought to enable efficient information processing and information transfer across distal regions in the brain (Changeux and Danchin 1976; Goldman-Rakic 1987; Huttenlocher 1990; Benes et al. 1994; Paus et al. 1999; Casey et al. 2005). Also consistent with this suggestion is the observation that FA, as measured by DTI, shows continued increases during adolescence and early adulthood within a number of WM tracts that subserve communication between distal regions of cortex, including the inferior fronto-occipital, superior longitudinal and uncinate fasciculi (Olesen et al. 2003; Snook et al. 2005; Zhang et al. 2005; Liston et al. 2006; Eluvathingal et al. 2007; Giorgio et al. 2008).

However, we agree with Fair et al. (2007, 2008) in acknowledging that WM structural changes alone are likely not sufficient to explain these results. Instead, given that the interregional correlations that form the basis for ICNs are thought to reflect a long-standing history of neuronal/regional coactivation (Dosenbach et al. 2007; Fair et al. 2007; Pinsk and Kastner 2007), age-related changes in ICN FC may reflect experience-related changes in the patterns of regional coactivation elicited by evoked (cognitive-, sensory-, and motor-driven) activity in large-scale functional networks. Such evoked activity is thought to play a central role in determining which synaptic connections persist and which are eliminated during development (Changeux and Danchin 1976; Rakic et al. 1994; Innocenti and Price 2005). Thus, evoked activity impacts upon both the structural and functional organization of the brain, and this mutual influence may be reflected in the organization of ICNs detected using FC analyses. Without the ability to directly examine the links between these microstructural, macrostructural and functional observations, these suggestions are speculative. Nonetheless, future studies, particularly longitudinal studies in nonhuman primates, may provide support for these speculations.

Developmental Changes in Default-Mode FC

The developmental changes in FC were most striking for seeds S7 and I9; whereas strong positive correlation between these seeds and the posterior cingulate/precuneus and temporoparietal cortex was evident in adults, they were not observed in children. Ventromedial PFC, posterior cingulate, precuneus and temporoparietal cortex are core nodes of the "default-mode" network, an ICN that has received considerable recent attention (Raichle et al. 2001; Fox and Raichle 2007), due to its high metabolic activity at rest and its implication in social

cognitive processes (e.g., Gusnard et al. 2001; Uddin et al. 2007). The absence of significant anterior–posterior connections within this network in children is consistent with the findings of Fair et al. (2008, 2007), and with Fransson et al. (2007) who demonstrated that a sample of preterm infants also lacked anterior–posterior FC within the default-mode network. Other recent studies have also demonstrated that FC between the anterior and posterior nodes of the default-mode network is reduced in elderly, relative to young adults (Andrews-Hanna et al. 2007; Damoiseaux et al. 2007). Together, these findings suggest that anterior–posterior FC of the default-mode network follows an inverted-U-shaped developmental trajectory, whereby FC increases from childhood to adulthood but subsequently declines in old age. Furthermore, Hampson et al. (2006) recently found that accuracy in a working memory task was correlated with the strength of anterior–posterior FC within the default-mode network, suggesting that maturation of this network may impact cognitive, as well as social cognitive performance, a suggestion that merits further examination.

Caudal-Ventral Gradient of Developmental Changes

Cognitive developmental studies suggest that more sophisticated aspects of cognitive, emotional and social cognitive processing continue to undergo substantial development throughout adolescence and into adulthood (Nelson et al. 2003; Ernst et al. 2005; Steinberg 2005; Blakemore and Choudhury 2006; Crone et al. 2006; Davidson et al. 2006; Galvan et al. 2006; Thomas et al. 2007; Hare et al. 2008). In particular, cognitive and emotional functions, such as those involved in mood regulation, decision making and reward processing, appear inherent to behaviors which can become problematic in adolescence (e.g., substance abuse, risk-taking, mood disorders) (Dahl 2004; Steinberg 2005; Casey et al. 2008; Steinberg 2008). Such behaviors are thought to reflect immature functioning of cognitive, social and emotional networks (Steinberg 2005; Casey et al. 2008; Hare et al. 2008). In line with these studies, we observed a gradient of development, such that caudal and dorsal seeds (S1 and S3) showed less marked differences across the age groups, suggestive of more rapid maturation, than the ventromedial seeds (S7 and I9; see Figs 1 and 2), which showed significant monotonic changes in FC from childhood, through adolescence, to adulthood. The overall effects of age group on long-distance correlations (Figs 4 and 5 and Table 2) also support the gradient of development observable in the voxelwise results. The ICNs elicited by seeds S7 and I9 comprised a number of cortical and subcortical regions (e.g., subgenual cingulate/BA 25, ventral striatum and amygdala) central to the cognitive and emotional domains implicated in behaviors and disorders that onset during adolescence. For example, both major depressive disorder and substance abuse are extremely rare in childhood but increase sharply in incidence during adolescence (Angold et al. 1998; Costello et al. 2003).

In addition to task-based functional imaging studies which suggest a protracted developmental time course for emotional and social cognitive networks, there is also anatomical evidence for continued neuronal maturation of limbic and paralimbic systems into adulthood. For example, Benes et al. (1994) observed a 95% increase in the area of myelin staining in the superior medullary lamina of the hippocampus between the first and second decades of life, and continued myelination of this brain area was observed into the sixth decade. Interestingly, based on the anatomy of neuronal connections in the area, Benes et al. suggest that some of the myelinating axons in that region of the hippocampus may originate in the cingulate gyrus (likely the subgenual area—Carmichael and Price 1995a; Johansen-Berg et al. 2007). Finally, consistent with our suggestions, Benes et al. noted that the extended time course of myelination parallels the protracted development of emotional regulation.

Development of Laterality

Reduced lateralization of task-related activations in children and adolescents, relative to adults, has been observed in a number of attentional tasks (e.g., Bunge et al. 2002; Moses et al. 2002; Booth et al. 2003), and studies of language-related function (Holland et al. 2001; Szaflarski et al. 2006). Our data were consistent with these observations; for the ICNs associated with seeds S3 and S5, we observed strongly bilateral FC between the seed ROIs and lateral frontal regions in children, but increasing lateralization of these frontal correlations with age. Given that many functional networks, particularly those associated with aspects of language function, attention and cognitive control, are highly lateralized in adults (e.g., Aboitiz et al. 1995; Coull and Nobre 1998; Garavan et al. 1999; Corbetta and Shulman 2002; Toga and Thompson 2003), the age-related increases in lateralized FC strongly support our suggestion that measures of FC can provide an accurate reflection of maturational changes in functional networks. Interestingly, this developmental progression also mirrors the pattern of change seen in elderly adults, in whom decreasing lateralization of task-evoked activity is often observed (Cabeza 2002; Cabeza et al. 2002; Dolcos et al. 2002), consistent with the notion that brain functional organization demonstrates an inverse-U-shaped developmental trajectory across the lifespan.

Monotonic Changes in FC and Negatively Correlated Networks

Changes in brain functional organization during adolescence are assumed to reflect the transition between immature organization and efficient communication and collaboration among brain regions (Luna and Sweeney 2004). Our data were consistent with this interpretation. With few exceptions, the developmental changes in FC we identified were monotonic for the broad age groups we examined. Nonmonotonic changes in FC, whereby a different pattern was observed for the adolescent, relative to the adult and child groups, were most frequently observed in the negatively correlated networks, which appeared to undergo the most reorganization from childhood to adulthood. Although the functional importance of the negative relationships between networks remains unknown (Fox et al. 2005; Fox and Raichle 2007), the developmental sensitivity of these networks may represent a clue to their physiologic significance. Further, different patterns of task-evoked activity in adolescents, relative to children and adults, have been observed in several studies (McGivern et al. 2002; Galvan et al. 2006; Hare et al. 2008), and have been interpreted as reflecting some of the cognitive and emotional changes specific to adolescence (Casey et al. 2008). How such an interpretation relates to adolescent-specific patterns of FC merits further investigation.

Implications for Clinical Conditions

Perturbations of the maturational processes of synaptic pruning and myelination have been proposed to underlie developmental

pathologies, particularly autism (Piven et al. 1990; Courchesne et al. 2004, 2005; Hazlett et al. 2005) and schizophrenia (Feinberg 1982; McGlashan and Hoffman 2000; Thompson et al. 2004; Gogtay et al. 2007; Gogtay 2008). These theories are supported by neuroimaging data. For example, findings from a number of studies support the suggestion that neuronal connectivity in autism is characterized by a predominance of local neuronal connectivity and a lack of long-range connections between brain regions (Just et al. 2004, 2007; Courchesne et al. 2005, 2007). Similarly, Shaw et al. (2007) showed that attention-deficit/hyperactivity disorder was associated with a delay in cortical maturation, measured in terms of cortical gray matter thickness trajectories. This delay was most evident in prefrontal regions, including the ACC. These findings suggest the potential applicability of FC analyses, and specifically the methods outlined here, to the study of clinical populations. The acquisition of resting-state data from pediatric and clinical populations is less effortful, and less prone to confounding effects (such as floor, ceiling and practice effects), relative to task-based fMRI studies.

More generally, the current findings also raise an important caveat for FC studies in psychiatric populations. Given that the ICNs detected in children may differ considerably from those detected in adults, group differences robustly present in adult samples may be absent in a pediatric group. Thus researchers should exercise caution in the application of FC findings that are based on adult samples to the investigation of developmental psychopathologies.

Limitations and Future Directions

Although the basis of correlated low-frequency fluctuations in fMRI BOLD remains poorly understood, there is a growing consensus that at least some of the patterns of coherent spontaneous activity track real anatomic connections between neurons (both mono- and polysynaptic), and reflect functional communications among neurons and neuronal assemblies that may serve to organize and coordinate their activity (Leopold et al. 2003; Buzsaki 2006; Raichle and Mintun 2006; Buckner and Vincent 2007; Fox and Raichle 2007; Pinsk and Kastner 2007; Raichle and Snyder 2007; Cohen et al. forthcoming). In the present study, we have observed that developmental changes in FC may represent an index of microstructural processes of brain maturation. Of course, as Rapoport and Gogtay (2008) noted, MRI does not give us direct access to such cellular changes, but the field of developmental neuroscience has developed a "shorthand" of interpreting the changes observed using MRI in terms of the purported underlying microstructural processes of synaptic production and elimination. Clearly, considerable further work is required, particularly in animals, to bolster our claim that FC analyses of resting-state BOLD data can provide a good indirect measure of these processes.

One step in that direction will be relating FC measures to indices of behavior and individual differences (Hampson et al. 2006; Fox et al. 2007; Seeley et al. 2007; Kelly et al. 2008). Several studies have already observed correlations between age-related changes in structural measures thought to reflect myelination and synaptic pruning and age-related improvements in cognitive functions such as working memory (Sowell et al. 2001; Olesen et al. 2003; Nagy et al. 2004; Liston et al. 2006). The investigation of links between cognitive development and FC measures represents an exciting avenue for future research, particularly in light of hypotheses concerning immature cognitive and emotional networks and problem behavior in adolescence (e.g., Steinberg 2005; Casey et al. 2008).

In the present study, we were able to identify significant voxelwise age-related differences in FC despite the small sample employed. This suggests that the effects observed are likely robust. Nonetheless, the true test of the present findings will be confirmation within a longitudinal design. More generally, determining the quantitative reliability of FC measures remains a high priority. Although the spatial organization of ICNs, such as the default-mode and "task positive" networks, is highly replicable across samples (Beckmann et al. 2005; Damoiseaux et al. 2006; De Luca et al. 2006; Fox et al. 2006), the temporal stability of specific patterns of FC has not yet been demonstrated. Finally, application of these methods to the study of clinical populations will allow for the investigation of their ability to detect patterns of hyper- and hypoconnectivity that have been hypothesized on the basis of structural MRI findings (Just et al. 2004; Liang et al. 2006; Garrity et al. 2007; Just et al. 2007; Kennedy and Courchesne 2007; Koshino et al. 2007).

Concluding Remarks

We examined the development of FC within 5 functionally distinct cingulate-based ICNs from late childhood through adolescence to early adulthood. Over this period we observed a significant age-related shift in the patterns of FC associated with each ACC seed. Although children demonstrated a pattern of diffuse correlations with voxels proximal to the seed ROI (i.e., greater local FC), adult ICNs were characterized by more focal patterns of local correlations and a greater number of significant correlations between the seed ROI and distal voxels. We suggest that this developmental trajectory is consistent with the patterns of age-related changes in the brain's structural and functional organization as demonstrated by post-mortem histological studies and structural and functional neuroimaging studies. Our data are also consistent with cognitive developmental studies that suggest an extended developmental time course for social cognitive and emotional functions, relative to aspects of motor and attentional control. Consequently, we suggest that measures of FC may represent an index of brain maturation, allowing us to track the purported underlying processes of microstructural maturation, with utility for the investigation of development, as well as developmental psychopathologies.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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Notes

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References

Aboitiz F, Ide A, Navarrete A, Pena M, Rodriguez E, Wolff V, Zaidel E. 1995. The anatomical substrates for language and hemispheric specialization. Biol Res. 28:45–50.

Amodio DM, Frith CD. 2006. Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci. 7:268–277.

Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, Buckner RL. 2007. Disruption of large-scale brain systems in advanced aging. Neuron. 56:924–935.

Angold A, Costello EJ, Worthman CM. 1998. Puberty and depression: the roles of age, pubertal status and pubertal timing. Psychol Med. 28:51–61.

Bartzokis G, Beckson M, Lu PH, Nuechterlein KH, Edwards N, Mintz J. 2001. Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. Arch Gen Psychiatry. 58:461–465.

Beckmann CF, De Luca M, Devlin JT, Smith SM. 2005. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci. 360:1001–1013.

Benes FM, Turtle M, Khan Y, Farol P. 1994. Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. Arch Gen Psychiatry. 51:477–484.

Biswal B, Yetkin FZ, Haughton VM, Hyde JS. 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 34:537–541.

Blakemore SJ, Choudhury S. 2006. Development of the adolescent brain: implications for executive function and social cognition. J Child Psychol Psychiatry. 47:296–312.

Booth JR, Burman DD, Meyer JR, Lei Z, Trommer BL, Davenport ND, Li W, Parrish TB, Gitelman DR, Mesulam MM. 2003. Neural development of selective attention and response inhibition. Neuroimage. 20:737–751.

Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD. 1999. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature. 402:179–181.

Botvinick MM, Cohen JD, Carter CS. 2004. Conflict monitoring and anterior cingulate cortex: an update. Trends Cogn Sci. 8:539–546.

Bourgeois JP, Goldman-Rakic PS, Rakic P. 1994. Synaptogenesis in the prefrontal cortex of rhesus monkeys. Cereb Cortex. 4:78–96.

Bourgeois JP, Rakic P. 1993. Changes of synaptic density in the primary visual cortex of the macaque monkey from fetal to adult stage. J Neurosci. 13:2801–2820.

Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A. 2001. Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. Cereb Cortex. 11:825–836.

Brett M, Johnsrude IS, Owen AM. 2002. The problem of functional localization in the human brain. Nat Rev Neurosci. 3:243–249.

Brody BA, Kinney HC, Kloman AS, Gilles FH. 1987. Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. J Neuropathol Exp Neurol. 46:283–301.

Brown TT, Lugar HM, Coalson RS, Miezin FM, Petersen SE, Schlaggar BL. 2005. Developmental changes in human cerebral functional organization for word generation. Cereb Cortex. 15:275–290.

Buckner RL, Vincent JL. 2007. Unrest at rest: The importance of default activity and spontaneous network correlations. Neuroimage. doi:10.1016/j.neuroimage.2007.01.010.

Bunge SA, Dudukovic NM, Thomason ME, Vaidya CJ, Gabrieli JDE. 2002. Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. Neuron. 33:301–311.

Bush G, Luu P, Posner MI. 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci. 4:215–222.

Buzsaki G. 2006. Rhythms of the brain. New York: Oxford University Press.

Cabeza R. 2002. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging. 17:85–100.

Cabeza R, Anderson ND, Locantore JK, McIntosh AR. 2002. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage. 17:1394–1402.

Carmichael ST, Price JL. 1995a. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. J Comp Neurol. 363:615–641.

Carmichael ST, Price JL. 1995b. Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. J Comp Neurol. 363:642–664.

Casey BJ, Getz S, Galvan A. 2008. The adolescent brain. Dev Rev. 28:62–77.

Casey BJ, Tottenham N, Liston C, Durston S. 2005. Imaging the developing brain: what have we learned about cognitive development? Trends Cogn Sci. 9:104–110.

Casey BJ, Trainor RJ, Orendi JL, Schubert AB, Nystrom LE, Giedd JN, Castellanos FX, Haxby JV, Noll DC, Cohen JD, et al. 1997. A developmental functional MRI study of prefrontal activation during performance of a Go-No-Go task. J Cogn Neurosci. 9:835–847.

Changeux JP, Danchin A. 1976. Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks. Nature. 264:705–712.

Chouinard PA, Paus T. 2006. The primary motor and premotor areas of the human cerebral cortex. Neuroscientist. 12:143–152.

Chugani HT, Phelps ME, Mazziotta JC. 1987. Positron emission tomography study of human brain functional development. Ann Neurol. 22:487–497.

Church JA, Coalson RS, Lugar HM, Petersen SE, Schlaggar BL. 2008. A developmental fmri study of reading and repetition reveals changes in phonological and visual mechanisms over age. Cereb Cortex. Advance Access published on January 31, 2008, doi:10.1093/cercor/bhm228.

Cohen AL, Fair DA, Dosenbach NUF, Miezin FM, Dierker D, Van Essen DC, Schlaggar BL, Petersen SE. Forthcoming. Defining functional areas in individual human brains using resting functional connectivity MRI. Neuroimage. 41:45–57.

Collett D. 2003. Modelling binary data. Boca Raton: Chapman & Hall/CRC.

Corbetta M, Shulman GL. 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci. 3:201–215.

Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. 2003. Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry. 60:837–844.

Coull JT, Nobre AC. 1998. Where and when to pay attention: the neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI. J Neurosci. 18:7426–7435.

Courchesne E, Pierce K, Schumann CM, Redcay E, Buckwalter JA, Kennedy DP, Morgan J. 2007. Mapping early brain development in autism. Neuron. 56:399–413.

Courchesne E, Redcay E, Kennedy DP. 2004. The autistic brain: birth through adulthood. Curr Opin Neurol. 17:489–496.

Courchesne E, Redcay E, Morgan JT, Kennedy DP. 2005. Autism at the beginning: microstructural and growth abnormalities underlying the cognitive and behavioral phenotype of autism. Dev Psychopathol. 17:577–597.

Cox RW. 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res. 29:162–173.

Crone EA, Donohue SE, Honomichl R, Wendelken C, Bunge SA. 2006. Brain regions mediating flexible rule use during development. J Neurosci. 26:11239–11247.

Curtis CE. 2006. Prefrontal and parietal contributions to spatial working memory. Neuroscience. 139:173–180.

Dahl RE. 2004. Adolescent brain development: a period of vulnerabilities and opportunities. Keynote address. Ann N Y Acad Sci. 1021:1–22.

Damoiseaux JS, Beckmann CF, Arigita EJS, Barkhof F, Scheltens P, Stam CJ, Smith SM, Rombouts SARB. 2007. Reduced resting-state brain activity in the "default network" in normal aging. Cereb Cortex. Advance Access published on December 5, 2007, doi:10.1093/cercor/bhm207.

Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF. 2006. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci USA. 103:13848–13853.

Davidson MC, Amso D, Anderson LC, Diamond A. 2006. Development of cognitive control and executive functions from 4 to 13 years: evidence from manipulations of memory, inhibition, and task switching. Neuropsychologia. 44:2037–2078.

De Luca M, Beckmann CF, De Stefano N, Matthews PM, Smith SM. 2006. fMRI resting state networks define distinct modes of long-distance interactions in the human brain. Neuroimage. 29:1359–1367.

Di Martino A, Scheres A, Margulies DS, Kelly AMC, Uddin LQ, Shehzad Z, Biswal B, Walters JR, Castellanos FX, Milham MP. 2008. Functional connectivity of human striatum: a resting state fMRI study. Cereb Cortex. Epub: April 9, 2008.
Dolcos F, Rice HJ, Cabeza R. 2002. Hemispheric asymmetry and aging: right hemisphere decline or asymmetry reduction. Neurosci Biobehav Rev. 26:819–825.
Dosenbach NU, Fair DA, Cohen AL, Schlaggar BL, Petersen SE. 2008. A dual-networks architecture of top-down control. Trends Cogn Sci. 12:99–105.
Dosenbach NUF, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RAT, Fox MD, Snyder AZ, Vincent JL, Raichle ME, et al. 2007. Distinct brain networks for adaptive and stable task control in humans. Proc Natl Acad Sci USA. 104:11073–11078.
Dosenbach NUF, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, Burgund ED, Grimes AL, Schlaggar BL, Petersen SE. 2006. A core system for the implementation of task sets. Neuron. 50:799–812.
Drevets WC, Price JL, Simpson JR, Jr, Todd RD, Reich T, Vannier M, Raichle ME. 1997. Subgenual prefrontal cortex abnormalities in mood disorders. Nature. 386:824–827.
Dum RP, Strick PL. 1991. The origin of corticospinal projections from the premotor areas in the frontal lobe. J Neurosci. 11:667–689.
Durston S, Casey BJ. 2006. What have we learned about cognitive development from neuroimaging? Neuropsychologia. 44:2149–2157.
Durston S, Davidson MC, Tottenham N, Galvan A, Spicer J, Fossella JA, Casey BJ. 2006. A shift from diffuse to focal cortical activity with development. Dev Sci. 9:1–8.
Elliott R, Dolan RJ, Frith CD. 2000. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cereb Cortex. 10:308–317.
Eluvathingal TJ, Hasan KM, Kramer L, Fletcher JM, Ewing-Cobbs L. 2007. Quantitative diffusion tensor tractography of association and projection fibers in normally developing children and adolescents. Cereb Cortex. 17:2760–2768.
Ernst M, Nelson EE, Jazbec S, McClure EB, Monk CS, Leibenluft E, Blair J, Pine DS. 2005. Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. Neuroimage. 25:1279–1291.
Fair DA, Cohen AL, Dosenbach NU, Church JA, Miezin FM, Barch DM, Raichle ME, Petersen SE, Schlaggar BL. 2008. The maturing architecture of the brain's default network. Proc Natl Acad Sci USA. 105:4028–4032.
Fair DA, Dosenbach NUF, Church JA, Cohen AL, Brahmbhatt S, Miezin FM, Barch DM, Raichle ME, Petersen SE, Schlaggar BL. 2007. Development of distinct control networks through segregation and integration. Proc Natl Acad Sci USA. 104:13507–13512.
Feinberg I. 1982. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res. 17:319–334.
Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME. 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc Natl Acad Sci USA. 103:10046–10051.
Fox MD, Raichle ME. 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 8:700–711.
Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA. 102:9673–9678.
Fox MD, Snyder AZ, Vincent JL, Raichle ME. 2007. Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. Neuron. 56:171–184.
Fransson P. 2006. How default is the default mode of brain function? Further evidence from intrinsic BOLD signal fluctuations. Neuropsychologia. 44:2836–2845.
Fransson P, Skiold B, Horsch S, Nordell A, Blennow M, Lagercrantz H, Aden U. 2007. Resting-state networks in the infant brain. Proc Natl Acad Sci USA. 104:15531–15536.
Friston KJ, Frith CD, Liddle PF, Frackowiak RS. 1993. Functional connectivity: the principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab. 13:5–14.
Frith U, Frith CD. 2003. Development and neurophysiology of mentalizing. Philos Trans R Soc Lond B Biol Sci. 358:459–473.
Galvan A, Hare TA, Parra CE, Penn J, Voss H, Glover G, Casey BJ. 2006. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. J Neurosci. 26:6885–6892.
Garavan H, Ross TJ, Kaufman J, Stein EA. 2003. A midline dissociation between error-processing and response-conflict monitoring. Neuroimage. 20:1132–1139.
Garavan H, Ross TJ, Murphy K, Roche RA, Stein EA. 2002. Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. Neuroimage. 17:1820–1829.
Garavan H, Ross TJ, Stein EA. 1999. Right hemispheric dominance of inhibitory control: an event-related functional MRI study. Proc Natl Acad Sci USA. 96:8301–8306.
Garrity AG, Pearlson GD, McKiernan K, Lloyd D, Kiehl KA, Calhoun VD. 2007. Aberrant "default mode" functional connectivity in schizophrenia. Am J Psychiatry. 164:450–457.
Giedd JN. 2004. Structural magnetic resonance imaging of the adolescent brain. Ann N Y Acad Sci. 1021:77–85.
Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. 1999. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci. 2:861–863.
Giorgio A, Watkins KE, Douaud G, James AC, James S, De Stefano N, Matthews PM, Smith SM, Johansen-Berg H. 2008. Changes in white matter microstructure during adolescence. Neuroimage. 39:52–61.
Gogtay N. 2008. Cortical brain development in schizophrenia: insights from neuroimaging studies in childhood-onset schizophrenia. Schizophr Bull. 34:30–36.
Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF, 3rd, Herman DH, Clasen LS, Toga AW, et al. 2004. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci USA. 101: 8174–8179.
Gogtay N, Greenstein D, Lenane M, Clasen L, Sharp W, Gochman P, Butler P, Evans A, Rapoport J. 2007. Cortical brain development in nonpsychotic siblings of patients with childhood-onset schizophrenia. Arch Gen Psychiatry. 64:772–780.
Goldman-Rakic PS. 1987. Development of cortical circuitry and cognitive function. Child Dev. 58:601–622.
Goldman-Rakic PS, Brown RM. 1982. Postnatal development of monoamine content and synthesis in the cerebral cortex of rhesus monkeys. Brain Res. 256:339–349.
Greicius MD, Menon V. 2004. Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. J Cogn Neurosci. 16:1484–1492.
Greicius MD, Supekar K, Menon V, Dougherty RF. 2008. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex. Advance Access published on April 9, 2008, doi:10.1093/cercor/bhn059.
Gusnard DA, Akbudak E, Shulman GL, Raichle ME. 2001. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc Natl Acad Sci USA. 98:4259–4264.
Hampson M, Driesen NR, Skudlarski P, Gore JC, Constable RT. 2006. Brain connectivity related to working memory performance. J Neurosci. 26:13338–13343.
Hare TA, Tottenham N, Galvan A, Voss HU, Glover GH, Casey BJ. 2008. Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. Biol Psychiatry. 63:927–934.
Hazlett HC, Poe M, Gerig G, Smith RG, Provenzale J, Ross A, Gilmore J, Piven J. 2005. Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. Arch Gen Psychiatry. 62:1366–1376.
Hester RL, Murphy K, Foxe JJ, Foxe DM, Javitt DC, Garavan H. 2004. Predicting success: patterns of cortical activation and deactivation prior to response inhibition. J Cogn Neurosci. 16:776–785.

Holland SK, Plante E, Weber Byars A, Strawsburg RH, Schmithorst VJ, Ball WS, Jr. 2001. Normal fMRI brain activation patterns in children performing a verb generation task. Neuroimage. 14:837–843.
Huttenlocher PR. 1979. Synaptic density in human frontal cortex—developmental changes and effects of aging. Brain Res. 163:195–205.
Huttenlocher PR. 1990. Morphometric study of human cerebral cortex development. Neuropsychologia. 28:517–527.
Huttenlocher PR, Dabholkar AS. 1997. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol. 387:167–178.
Huttenlocher PR, de Courten C, Garey LJ, Van der Loos H. 1982. Synaptogenesis in human visual cortex—evidence for synapse elimination during normal development. Neurosci Lett. 33: 247–252.
Innocenti GM, Price DJ. 2005. Exuberance in the development of cortical networks. Nat Rev Neurosci. 6:955–965.
Jacobs B, Chugani HT, Allada V, Chen S, Phelps ME, Pollack DB, Raleigh MJ. 1995. Developmental changes in brain metabolism in sedated rhesus macaques and vervet monkeys revealed by positron emission tomography. Cereb Cortex. 5:222–233.
Johansen-Berg H, Gutman DA, Behrens TE, Matthews PM, Rushworth MF, Katz E, Lozano AM, Mayberg HS. 2008. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. Cereb Cortex. 18:1374–1383.
Johnson SC, Baxter LC, Wilder LS, Pipe JG, Heiserman JE, Prigatano GP. 2002. Neural correlates of self-reflection. Brain. 125:1808–1814.
Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ. 2007. Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an executive function task and corpus callosum morphometry. Cereb Cortex. 17:951–961.
Just MA, Cherkassky VL, Keller TA, Minshew NJ. 2004. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. Brain. 127:1811–1821.
Kang HC, Burgund ED, Lugar HM, Petersen SE, Schlaggar BL. 2003. Comparison of functional activation foci in children and adults using a common stereotactic space. Neuroimage. 19:16–28.
Kannurpatti SS, Biswal BB, Kim YR, Rosen BR. 2008. Spatio temporal characteristics of low frequency BOLD signal fluctuations in isoflurane anesthetized rat brain. Neuroimage. 40:1738–1747.
Kelly AMC, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. 2008. Competition between functional brain networks mediates behavioral variability. Neuroimage. 39:527–537.
Kennedy DP, Courchesne E. 2007. The intrinsic functional organization of the brain is altered in autism. Neuroimage. 39:1877–1885.
Kiehl KA, Liddle PF, Hopfinger JB. 2000. Error processing and the rostral anterior cingulate: an event-related fMRI study. Psychophysiology. 37:216–223.
Knutson B, Fong GW, Bennett SM, Adams CM, Hommer D. 2003. A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. Neuroimage. 18:263–272.
Koshino H, Kana RK, Keller TA, Cherkassky VL, Minshew NJ, Just MA. 2007. fMRI investigation of working memory for faces in autism: visual coding and underconnectivity with frontal areas. Cereb Cortex. 18:289–300.
Kroger JK, Sabb FW, Fales CL, Bookheimer SY, Cohen MS, Holyoak KJ. 2002. Recruitment of anterior dorsolateral prefrontal cortex in human reasoning: a parametric study of relational complexity. Cereb Cortex. 12:477–485.
LaMantia AS, Rakic P. 1994. Axon overproduction and elimination in the anterior commissure of the developing rhesus monkey. J Comp Neurol. 340:328–336.
Lambe EK, Krimer LS, Goldman-Rakic PS. 2000. Differential postnatal development of catecholamine and serotonin inputs to identified neurons in prefrontal cortex of rhesus monkey. J Neurosci. 20:8780–8787.
Leopold DA, Murayama Y, Logothetis NK. 2003. Very slow activity fluctuations in monkey visual cortex: implications for functional brain imaging. Cereb Cortex. 13:422–433.
Liang M, Zhou Y, Jiang T, Liu Z, Tian L, Liu H, Hao Y. 2006. Widespread functional disconnectivity in schizophrenia with resting-state functional magnetic resonance imaging. Neuroreport. 17:209–213.
Lidow MS, Goldman-Rakic PS, Rakic P. 1991. Synchronized overproduction of neurotransmitter receptors in diverse regions of the primate cerebral cortex. Proc Natl Acad Sci USA. 88:10218–10221.
Lidow MS, Rakic P. 1992. Scheduling of monoaminergic neurotransmitter receptor expression in the primate neocortex during postnatal development. Cereb Cortex. 2:401–416.
Liston C, Watts R, Tottenham N, Davidson MC, Niogi S, Ulug AM, Casey BJ. 2006. Frontostriatal microstructure modulates efficient recruitment of cognitive control. Cereb Cortex. 16:553–560.
Luna B, Sweeney JA. 2004. The emergence of collaborative brain function: FMRI studies of the development of response inhibition. Ann N Y Acad Sci. 1021:296–309.
Luo Q, Perry C, Peng D, Jin Z, Xu D, Ding G, Xu S. 2003. The neural substrate of analogical reasoning: an fMRI study. Brain Res Cogn Brain Res. 17:527–534.
Lutcke H, Frahm J. 2007. Lateralized anterior cingulate function during error processing and conflict monitoring as revealed by high-resolution fMRI. Cereb Cortex. 18:508–515.
Margulies DS, Kelly AMC, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. 2007. Mapping the functional connectivity of anterior cingulate cortex. Neuroimage. 37:579–588.
Mayberg HS. 2006. Defining neurocircuits in depression. Psychiatric Ann. 36:259–269.
McGivern RF, Andersen J, Byrd D, Mutter KL, Reilly J. 2002. Cognitive efficiency on a match to sample task decreases at the onset of puberty in children. Brain Cogn. 50:73–89.
McGlashan TH, Hoffman RE. 2000. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. Arch Gen Psychiatry. 57:637–648.
Milham MP, Banich MT. 2005. Anterior cingulate cortex: an fMRI analysis of conflict specificity and functional differentiation. Hum Brain Mapp. 25:328–335.
Milham MP, Banich MT, Webb A, Barad V, Cohen NJ, Wszalek T, Kramer AF. 2001. The relative involvement of anterior cingulate and prefrontal cortex in attentional control depends on nature of conflict. Brain Res Cogn Brain Res. 12:467–473.
Moses P, Roe K, Buxton RB, Wong EC, Frank LR, Stiles J. 2002. Functional MRI of global and local processing in children. Neuroimage. 16:415–424.
Nagy Z, Westerberg H, Klingberg T. 2004. Maturation of white matter is associated with the development of cognitive functions during childhood. J Cogn Neurosci. 16:1227–1233.
Nee DE, Wager TD, Jonides J. 2007. Interference resolution: insights from a meta-analysis of neuroimaging tasks. Cogn Affect Behav Neurosci. 7:1–17.
Nelson EE, McClure EB, Monk CS, Zarahn E, Leibenluft E, Pine DS, Ernst M. 2003. Developmental differences in neuronal engagement during implicit encoding of emotional faces: an event-related fMRI study. J Child Psychol Psychiatry. 44:1015–1024.
Ochsner KN, Beer JS, Robertson ER, Cooper JC, Gabrieli JD, Kihsltrom JF, D'Esposito M. 2005. The neural correlates of direct and reflected self-knowledge. Neuroimage. 28:797–814.
Ochsner KN, Gross JJ. 2005. The cognitive control of emotion. Trends Cogn Sci. 9:242–249.
Olesen PJ, Nagy Z, Westerberg H, Klingberg T. 2003. Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network. Brain Res Cogn Brain Res. 18:48–57.
Paulus MP, Frank LR. 2006. Anterior cingulate activity modulates nonlinear decision weight function of uncertain prospects. Neuroimage. 30:668–677.
Paulus MP, Hozack N, Frank L, Brown GG. 2002. Error rate and outcome predictability affect neural activation in prefrontal cortex and anterior cingulate during decision-making. Neuroimage. 15: 836–846.
Paus T. 2001. Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nat Rev Neurosci. 2:417–424.

Paus T, Zijdenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, Rapoport JL, Evans AC. 1999. Structural maturation of neural pathways in children and adolescents: in vivo study. Science. 283:1908–1911.
Petanjek Z, Judas M, Kostovic I, Uylings HB. 2008. Lifespan alterations of basal dendritic trees of pyramidal neurons in the human prefrontal cortex: a layer-specific pattern. Cereb Cortex. 18:915–929.
Phan KL, Wager T, Taylor SF, Liberzon I. 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage. 16:331–348.
Phillips ML, Drevets WC, Rauch SL, Lane R. 2003. Neurobiology of emotion perception I: The neural basis of normal emotion perception. Biol Psychiatry. 54:504–514.
Pinsk MA, Kastner S. 2007. Neuroscience—unconscious networking. Nature. 447:546–547.
Piven J, Berthier ML, Starkstein SE, Nehme E, Pearlson G, Folstein S. 1990. Magnetic resonance imaging evidence for a defect of cerebral cortical development in autism. Am J Psychiatry. 147:734–739.
Posner MI, Petersen SE. 1990. The attention system of the human brain. Annu Rev Neurosci. 13:25–42.
Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. 2001. A default mode of brain function. Proc Natl Acad Sci USA. 98:676–682.
Raichle ME, Mintun MA. 2006. Brain work and brain imaging. Annu Rev Neurosci. 29:449–476.
Raichle ME, Snyder AZ. 2007. A default mode of brain function: a brief history of an evolving idea. Neuroimage. 37:1083–1090discussion 1089–1097.
Rakic P, Bourgeois JP, Eckenhoff MF, Zecevic N, Goldman-Rakic PS. 1986. Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science. 232:232–235.
Rakic P, Bourgeois JP, Goldman-Rakic PS. 1994. Synaptic development of the cerebral cortex: implications for learning, memory, and mental illness. Prog Brain Res. 102:227–243.
Rapoport JL, Gogtay N. 2008. Brain neuroplasticity in healthy, hyperactive and psychotic children: insights from neuroimaging. Neuropsychopharmacology. 33:181–197.
Ridderinkhof KR, van der Molen MW, Band GP, Bashore TR. 1997. Sources of interference from irrelevant information: a developmental study. J Exp Child Psychol. 65:315–341.
Rilling JK, Barks SK, Parr LA, Preuss TM, Faber TL, Pagnoni G, Bremner JD, Votaw JR. 2007. A comparison of resting-state brain activity in humans and chimpanzees. Proc Natl Acad Sci USA. 104:17146–17151.
Rosenberg DR, Lewis DA. 1995. Postnatal maturation of the dopaminergic innervation of monkey prefrontal and motor cortices: a tyrosine hydroxylase immunohistochemical analysis. J Comp Neurol. 358:383–400.
Rueda MR, Fan J, McCandliss BD, Halparin JD, Gruber DB, Lercari LP, Posner MI. 2004. Development of attentional networks in childhood. Neuropsychologia. 42:1029–1040.
Rueda MR, Posner MI, Rothbart MK. 2005. The development of executive attention: contributions to the emergence of self-regulation. Dev Neuropsychol. 28:573–594.
Saad ZS, Reynolds RC, Argall B, Japee S, Cox RW. 2004. SUMA: an interface for surface-based intra- and inter-subject analysis with AFNI. IEEE International Symposium on Biomedical Imaging: Nano to Macro: 2:1510–1513.
Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci. 27:2349–2356.
Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, Clasen L, Evans A, Giedd J, Rapoport JL. 2007. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci USA. 104:19649–19654.
Snook L, Paulson LA, Roy D, Phillips L, Beaulieu C. 2005. Diffusion tensor imaging of neurodevelopment in children and young adults. Neuroimage. 26:1164–1173.
Sowell ER, Delis D, Stiles J, Jernigan TL. 2001. Improved memory functioning and frontal lobe maturation between childhood and adolescence: a structural MRI study. J Int Neuropsychol Soc. 7:312–322.
Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. 2003. Mapping cortical change across the human life span. Nat Neurosci. 6:309–315.
Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW. 1999. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. Nat Neurosci. 2:859–861.
Sowell ER, Thompson PM, Tessner KD, Toga AW. 2001. Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: inverse relationships during postadolescent brain maturation. J Neurosci. 21:8819–8829.
Sowell ER, Thompson PM, Toga AW. 2004. Mapping changes in the human cortex throughout the span of life. Neuroscientist. 10:372–392.
Steinberg L. 2005. Cognitive and affective development in adolescence. Trends Cogn Sci. 9:69–74.
Steinberg L. 2008. A social neuroscience perspective on adolescent risk-taking. Dev Rev. 28:78–106.
Szaflarski JP, Holland SK, Schmithorst VJ, Byars AW. 2006. fMRI study of language lateralization in children and adults. Hum Brain Mapp. 27:202–212.
Talairach J, Tournoux P. 1988. Co-planar stereotaxic atlas of the human brain. New York: Thieme Medical Publishers, Inc.
Tamm L, Menon V, Reiss AL. 2002. Maturation of brain function associated with response inhibition. J Am Acad Child Adolesc Psychiatry. 41:1231–1238.
Taylor SF, Martis B, Fitzgerald KD, Welsh RC, Abelson JL, Liberzon I, Himle JA, Gehring WJ. 2006. Medial frontal cortex activity and loss-related responses to errors. J Neurosci. 26:4063–4070.
Taylor SF, Stern ER, Gehring WJ. 2007. Neural systems for error monitoring: recent findings and theoretical perspectives. Neuroscientist. 13:160–172.
Thomas LA, De Bellis MD, Graham R, LaBar KS. 2007. Development of emotional facial recognition in late childhood and adolescence. Dev Sci. 10:547–558.
Thomason ME, Burrows BE, Gabrieli JD, Glover GH. 2005. Breath holding reveals differences in fMRI BOLD signal in children and adults. Neuroimage. 25:824–837.
Thompson PM, Hayashi KM, Sowell ER, Gogtay N, Giedd JN, Rapoport JL, de Zubicaray GI, Janke AL, Rose SE, Semple J, et al. 2004. Mapping cortical change in Alzheimer's disease, brain development, and schizophrenia. Neuroimage. 23(Suppl 1):S2–S18.
Toga AW, Thompson PM. 2003. Mapping brain asymmetry. Nat Rev Neurosci. 4:37–48.
Toro R, Fox PT, Paus T. 2008. Functional coactivation map of the human brain. Cereb Cortex. Epub: February 21, 2008.
Uddin LQ, Iacoboni M, Lange C, Keenan JP. 2007. The self and social cognition: the role of cortical midline structures and mirror neurons. Trends Cogn Sci. 11:153–157.
Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC, Zempel JM, Snyder LH, Corbetta M, Raichle ME. 2007. Intrinsic functional architecture in the anaesthetized monkey brain. Nature. 447:83–86.
Wager TD, Smith EE. 2003. Neuroimaging studies of working memory: a meta-analysis. Cogn Affect Behav Neurosci. 3:255–274.
Weissman DH, Roberts KC, Visscher KM, Woldorff MG. 2006. The neural bases of momentary lapses in attention. Nat Neurosci. 9:971–978.
Wenger KK, Visscher KM, Miezin FM, Petersen SE, Schlaggar BL. 2004. Comparison of sustained and transient activity in children and adults using a mixed blocked/event-related fMRI design. Neuroimage. 22:975–985.
Yakovlev PI, Lecours AR. 1967. The myelogenetic cycles of regional maturation of the brain. In: Minkowski A, editor. Regional development of the brain in early life. Oxford: Blackwell Scientific. p. 3–70.
Zhang LJ, Thomas KM, Davidson MC, Casey BJ, Heier LA, Ulug AM. 2005. MR quantitation of volume and diffusion changes in the developing brain. Am J Neuroradiol. 26:45–49.